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<b>(21) International Application Number:</b> PCT/SE97/01098 <b>(22) International Filing Date:</b> 18 June 1997 (18.06.97)  <b>(30) Priority Data:</b> 9602442-7                      20 June 1996 (20.06.96)                      SE  <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CEDERBERG, Christer [SE/SE]; Åkergatan 1, S-431 69 Mölndal (SE). SACHS, George [US/US]; 17986 Boris Drive, Encino, CA 91316 (US).  <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> ADMINISTRATION REGIMEN OF H <sup>+</sup> , K <sup>+</sup> -ATPase INHIBITORS		
<b>(57) Abstract</b>  A new administration regimen giving an extended plasma concentration profile of a H <sup>+</sup> , K <sup>+</sup> -ATPase inhibitor. The extended plasma profile is received by two or more consecutive administrations of a unit dose of a H <sup>+</sup> , K <sup>+</sup> -ATPase with 0.5-4 hours interval or by a pharmaceutical composition with extended release, which may be administered once daily.		

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**ADMINISTRATION REGIMEN OF  $H^+$ ,  $K^+$ -ATPase INHIBITORS**Field of the invention

5 The present invention is related to a new administration regimen of proton pump inhibitors, i.e.  $H^+$ ,  $K^+$ -ATPase inhibitors. The new administration regimen gives an extended blood plasma concentration profile of the pharmaceutical substance, i.e. the proton pump inhibitors, thereby giving an improved inhibition of gastric acid secretion and an improved therapeutic effect. More specifically, the invention refers to the use of pharmaceutical  
10 preparations with a controlled release in the treatment of gastric acid-related diseases. The pharmaceutical preparation is preferably in the form of a dosage form which provides an extended and constant release of the acid labile  $H^+$ ,  $K^+$ -ATPase inhibitor in the small and/or large intestines (but not in stomach) or a dosage form which provides two or more discrete pulses of release of the  $H^+$ ,  $K^+$ -ATPase inhibitor in the small and/or large  
15 intestines (but not in stomach) separated in time with 0.5 - 4 hours. Furthermore, the present invention refers to the manufacture of such preparations.

Background of the invention

20 Acid labile  $H^+$ ,  $K^+$ -ATPase inhibitors also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole. Some of these compounds are for instance disclosed in EP-A1-0005129, WO 94/27988, EP-A1-174726, EP-A1-166287 and GB 2163747.

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These pharmaceutical substances are useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, they may be used for prevention and treatment of

gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrom.

Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with  
5 Non Ulcer Dyspepsia, and in patients with symptomatic gastro-esophageal reflux disease.

They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to  
10 these.

Therapeutic control of gastric acid secretion is fundamental in all these diseases, but the degree and duration of acid inhibition required for optimal clinical effect is not fully understood.

The duration of acid inhibition of one proton pump inhibitor such as for instance omeprazole is 3 - 4 days despite a plasma half-life of only 0.5 - 1 hour (Lind et al, Gut 1983;24:270-276)). This lack of temporal relationship between plasma concentration of omeprazole and the degree of acid inhibition is due to the long-lasting binding of the active  
20 inhibitor to the gastric pump.

Proton pump inhibitors, such as the above discussed omeprazole, are generally administered as a single daily dose of 20 mg to 40 mg, depending on the gastrointestinal disorder as well as the severity of the disease. In the treatment of Zollinger-Ellison  
25 syndrom higher dosages of 60 - 120 mg/daily and as much as 360 mg/daily have been used. Generally, the proton pump inhibitor is administered to the patient during 2 - 4 weeks, in some cases up to 8 weeks. Omeprazole has also been used as maintainace therapy for peptic ulcer disease and reflux oesophagitis during many years.

30 Despite this long duration of acid inhibition once daily dosing results in not more than



70-80 % inhibition of maximal acid output prior to next dose. Results from *Helicobacter pylori* eradication studies have shown an improved efficacy with twice daily dosing in combination with antimicrobials. Treatment of severe GORD is also improved by divided doses as compared to single daily dose increments. These improved clinical effects are due to longer periods of high acid inhibition.

Although action of proton pump inhibitors is covalent, efficacy depends on active pumps and there are two pools of pumps, active and inactive. Only active pumps are covalently inhibited. The inactive pumps are recruited throughout the day therefore effectiveness of acid inhibition improves for 72 hours on once a day treatment, steady state being achieved as a balance between inhibition of active pumps and *de novo* biosynthesis or reversal of inhibition.

Extended release formulations to give blood plasma levels extending from 6-12 hours (by any of several means) will result in a larger fraction of the pumps being inhibited and should result in more effective inhibition of acid secretion resulting in improved efficacy in GORD, more rapid healing of gastric ulcer and improved eradication of *H. Pylori*.

#### Detailed description of the drawings

Figure 1 shows two graphs. These show the differences between once daily administration and administration of two consecutive doses within 3 hours.

#### Summary of the invention

On a once a day administration regimen the maximal effect of omeprazole is about 75 % to 80 %, 24 hours after dose (Lind et al 1986, Scand J Gastroenterol (Suppl 118): 137 - 8 and Lind et al 1988, Scand J Gastroenterol 23: 1259 - 66), i.e. about 20 % to 25 % of the maximal gastric acid secretory capacity is present 24 hours after the dose. Even if an increased dose quantity of the proton pump inhibitor has been used (See Lind et al) the maximal gastric acid inhibition is limited to about 80 %.

The known dose dependency of gastric acid inhibition has hitherto resulted in a recommendation to initially increase the dose of the proton pump inhibitor, if a low response on the therapy or lack of response is obtained.

5

It has now been proposed according to the present invention to extend the plasma concentration profile of proton pump inhibitors and thereby improving their therapeutic effect. According to one aspect of the invention the extended plasma profile is provided by once daily administration of a dosage form which releases the proton pump inhibitor with an almost constant rate during an extended time period. According to another aspect of the invention the extended plasma profile is provided by once daily administration of a dosage form which, in the small and/or large intestines (but not in the stomach), releases the proton pump inhibitor in discrete pulses separated in time by 0.5 - 4 hours. It is also possible to obtain an extended plasma profile of a proton pump inhibitor by consecutive administrations of two or more unit doses with 0.5 - 4 hours intervals.

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#### Detailed description of the invention

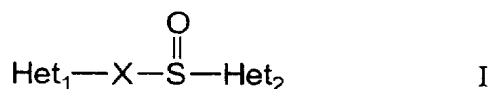
Acid secretion by the gastric mucosa is a property of the parietal cell. Whereas the functional regulation of this cell is a complicated process involving several different cell types with different receptors, acid transport *per se* is the property of a single P-type ATPase, the gastric  $H^+$ ,  $K^+$ -ATPase. Therefore, effective therapeutic control of acid secretion involves either receptor blockade or gastric  $H^+$ ,  $K^+$ -ATPase inhibition. This invention relates to the proton pump inhibitors and their reaction with the gastric acid pump. The half-life in plasma of the proton pump inhibitors is rather short. The administered proton pump inhibitor reacts with the active gastric acid pumps available for inhibition during that time. Un-inhibited, inactive pumps will be present during this time and pumps will recover following biosynthesis and reversal of inhibition. Therefore, by a repeated regimen or a dosage form which provides an extended plasma profile of the proton pump inhibitors recovered pumps as well as un-inhibited pumps not previously

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available will react with the newly administered dose or pulse of pharmaceutical substance or the continuously released substance.

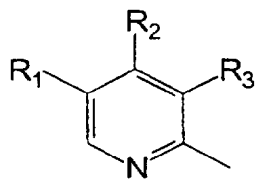
By administration of a pharmaceutical dosage form with an extended release, the plasma concentration of the pharmaceutical substance can be kept on a high level during an extended time. As a result the number of pumps inhibited by the proton pump inhibitor will increase and a more efficient therapeutic control of acid secretion will be obtained.

Compounds of interest for the novel administration with a repeated dosing regimen as well as for the controlled release preparations/compositions giving an extended plasma profile according to the present invention are compounds of the general formula I

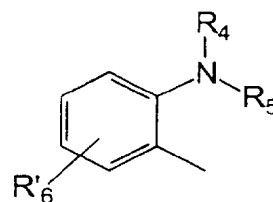


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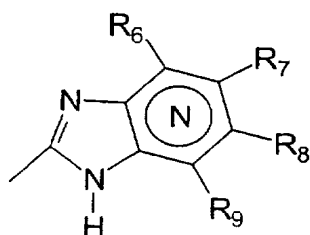
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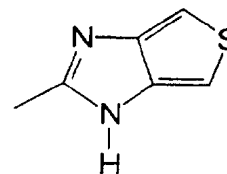
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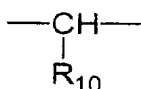
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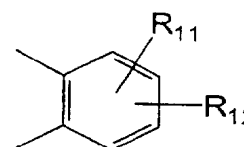
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X =



or



wherein

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N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

10 R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

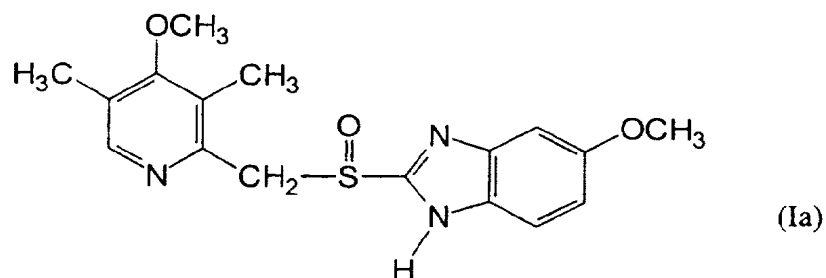
15 R<sub>6</sub>' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R<sub>6</sub>-R<sub>9</sub> form ring structures which may be further substituted;

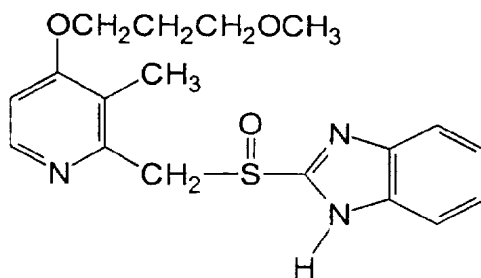
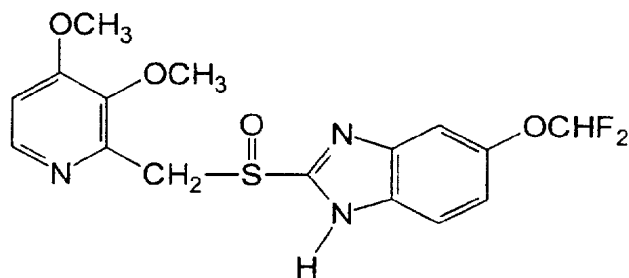
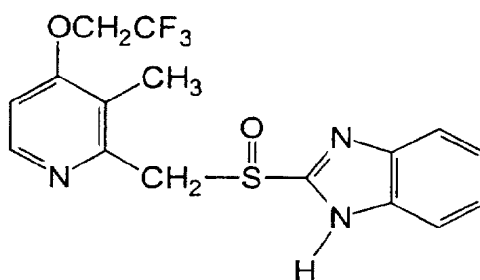
20 R<sub>10</sub> is hydrogen or forms an alkylene chain together with R<sub>3</sub> and

$R_{11}$  and  $R_{12}$  are the same or different and selected from hydrogen, halogen or alkyl.

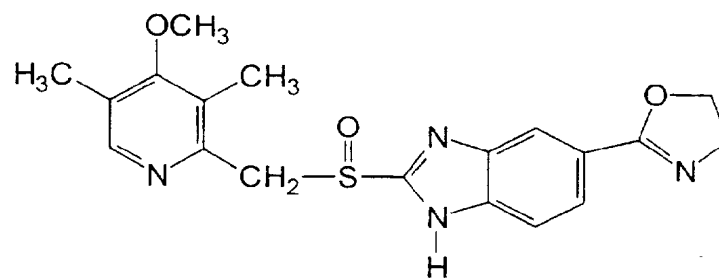
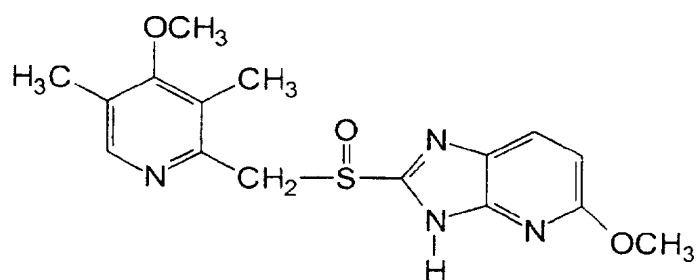
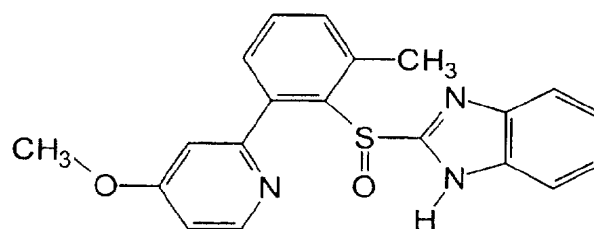
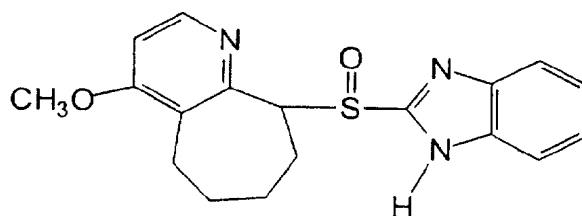
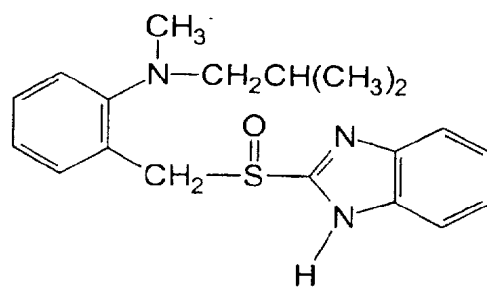
Examples of specifically interesting compounds according to formula I are

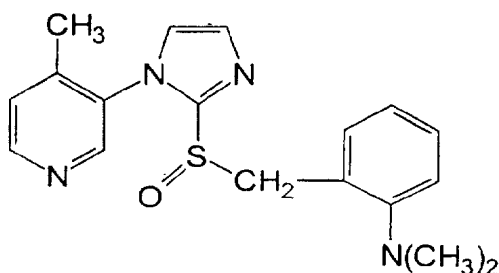


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The compound used in the administration regimen as well as in the controlled release preparations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Na}^{+}$  or  $\text{K}^{+}$  salts, preferably the  $\text{Mg}^{2+}$  salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

Preferred compounds for the administration regimen and the oral pharmaceutical preparation according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. Thus, the substances being acid labile proton pump inhibitors are best protected from contact with acidic gastric juice by an enteric coating. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230. An enteric coated tablet of omeprazole magnesium salt is described in WO 95/ 01783. A tableted multiple unit dosage form of omeprazole is described in WO 96/ 01623. Pharmaceutical preparations manufactured according to known principles as described in the specifications US-A 4,853,230, WO 95/ 01783 and WO 96/ 01623, hereby incorporated in whole by references, may be used for administration with an increased dosing frequency according to the present invention.

A unit dosage of the proton pump inhibitor, for instance 1 - 500 mg is administered at least twice a day. The unit dosage may be given with a dosing frequency of about 0.5 - 4 hours, preferably two doses are given during a time period of 2 to 3 hours. Suitable doses comprise for instance 5, 10, 15, 20, 30 and 40 mg of the pharmaceutical substance.

In another embodiment of the invention an extended plasma profile is obtained by administration of a unit dose of a proton pump inhibitor which releases the drug for absorption in the small and/or large intestines in discrete pulses separated in time by 0.5 - 4 hours.

Alternatively, an oral pharmaceutical formulation with extended release of the pharmaceutical substance during 2 - 12 hours, preferably 4 - 8 hours may be administered. Such an extended release preparation may comprise up to 500 mg of the substance, preferably the doses comprise about 5 - 100 mg of the substance, and more preferably 10 - 80 mg.

Different techniques for manufacturing of various controlled release preparations are for example described in Aulton M.E. (Churchill Livingstone Ed.), *Pharmaceutics: The science of dosage form design* (1988), p. 316-321.

The invention is described more in detail by the following examples.

### Examples

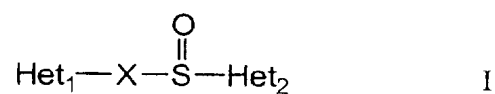
Omeprazole (Prilosec<sup>®</sup> capsules) 40 mg once daily (administered at 8.00 a.m.) or 20 mg given twice daily (administered at 8.00 a.m. and at 11.00 a.m.) given during five consecutive days were compared regarding effect on peptone stimulated gastric acid secretion and intragastric acidity measured on days 1 to 3 and day 5 in eight healthy subjects. During the first two days of treatment there was a significantly ( $p > 0.05$ ) lower number of hours with high acidity ( $\text{pH} > 1$ ) when omeprazole was given twice daily, 20 mg administered with 3 hours apart, compared to a single morning dose of 40 mg. There was



also a significantly higher degree of inhibition of peptone stimulated acid output 24 hours post dose during the first three days of treatment. See Figure 1. These results clearly support the concept of extended plasma profiles of omeprazole being beneficial in optimising control of acid secretion.

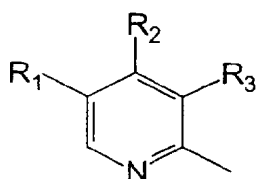
Claims

1. An administration regimen giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor, characterized in that the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound with the formula I

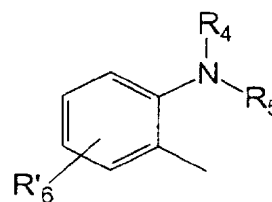


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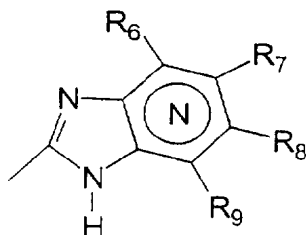
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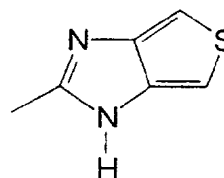
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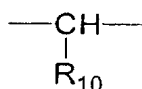
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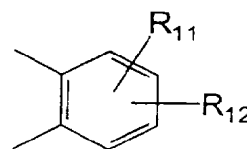
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R<sub>6</sub>-

5 R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

10

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

R<sub>6</sub>' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-

15 alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R<sub>6</sub>-R<sub>9</sub> form ring structures which may be further substituted;

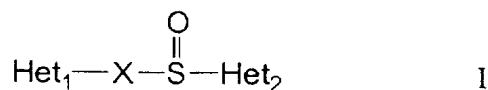
R<sub>10</sub> is hydrogen or forms an alkylene chain together with R<sub>3</sub> and

20 R<sub>11</sub> and R<sub>12</sub> are the same or different and selected from hydrogen, halogen or alkyl.

2. An administration regimen according to claim 1 characterized in that the H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor is a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

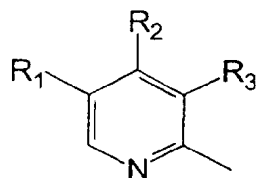
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3. An administration regimen giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor according to any of claims 1 and 2 characterized in that the extended plasma profile is obtained by two or more consecutive oral administrations of a unit dose of the  $H^+$ ,  $K^+$ -ATPase inhibitor with 0.5 - 4 hours intervals.
4. An administration regimen giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor according to claim 1 characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical preparation which releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.
5. An administration regimen according to claim 1, characterized in that the extended plasma profile is obtained by oral administration of a unit dose of a pharmaceutical preparation which releases the  $H^+$ ,  $K^+$ -ATPase inhibitor for absorption with an almost constant rate during an extended time period.
6. An administration regimen according to any of claims 1 - 5 characterized in that the extended plasma profile is received during 2 - 12 hours.
7. An oral pharmaceutical composition giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor, characterized in that the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound with the formula I

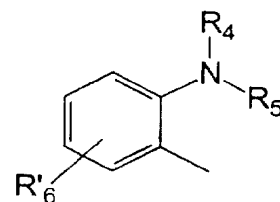


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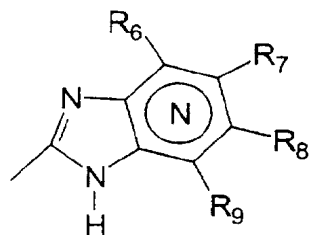
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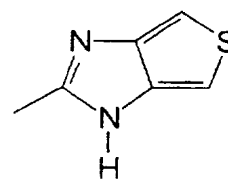
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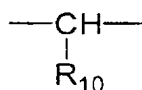
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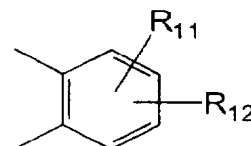
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wherein

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N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any substituents;

15 R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen, alkyl and aralkyl;

$R_6'$  is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

$R_6$ - $R_9$  are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups  $R_6$ - $R_9$  form ring structures which may be further substituted;

$R_{10}$  is hydrogen or forms an alkylene chain together with  $R_3$  and

$R_{11}$  and  $R_{12}$  are the same or different and selected from hydrogen, halogen or alkyl.

8. An oral pharmaceutical preparation according to claim 7, characterized in that the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

9. An oral pharmaceutical preparation giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor according to claim 7 characterized in that the pharmaceutical preparation releases the drug for absorption in two or more discrete pulses separated in time by 0.5 - 4 hours.

10. An oral pharmaceutical preparation according to claim 7, characterized in that the pharmaceutical preparation releases the  $H^+$ ,  $K^+$ -ATPase inhibitor for absorption with an almost constant rate during an extended time period.

11. An oral pharmaceutical preparation giving an extended blood plasma profile of a  $H^+$ ,  $K^+$ -ATPase inhibitor according to any of claims 7 - 10 characterized in that the extended plasma profile is received during 2 - 12 hours.

12. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

5 13. Use of an oral pharmaceutical composition as claimed in any of claims 7 - 10 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

14. Use of  $H^+$ ,  $K^+$  - ATPase inhibitor with the formula I defined in claim 1, for the  
10 preparation of a pharmaceutical composition with extended release.

15. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any of claims 7 - 10.

15

16. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any claims 7 - 10.

20 17. A method for receiving an extended plasma profile of a  $H^+$ ,  $K^+$  - ATPase inhibitor by administering to a patient in need thereof a pharmaceutical preparation with extended release of a  $H^+$ ,  $K^+$  - ATPase inhibitor as defined in claim 1.

25

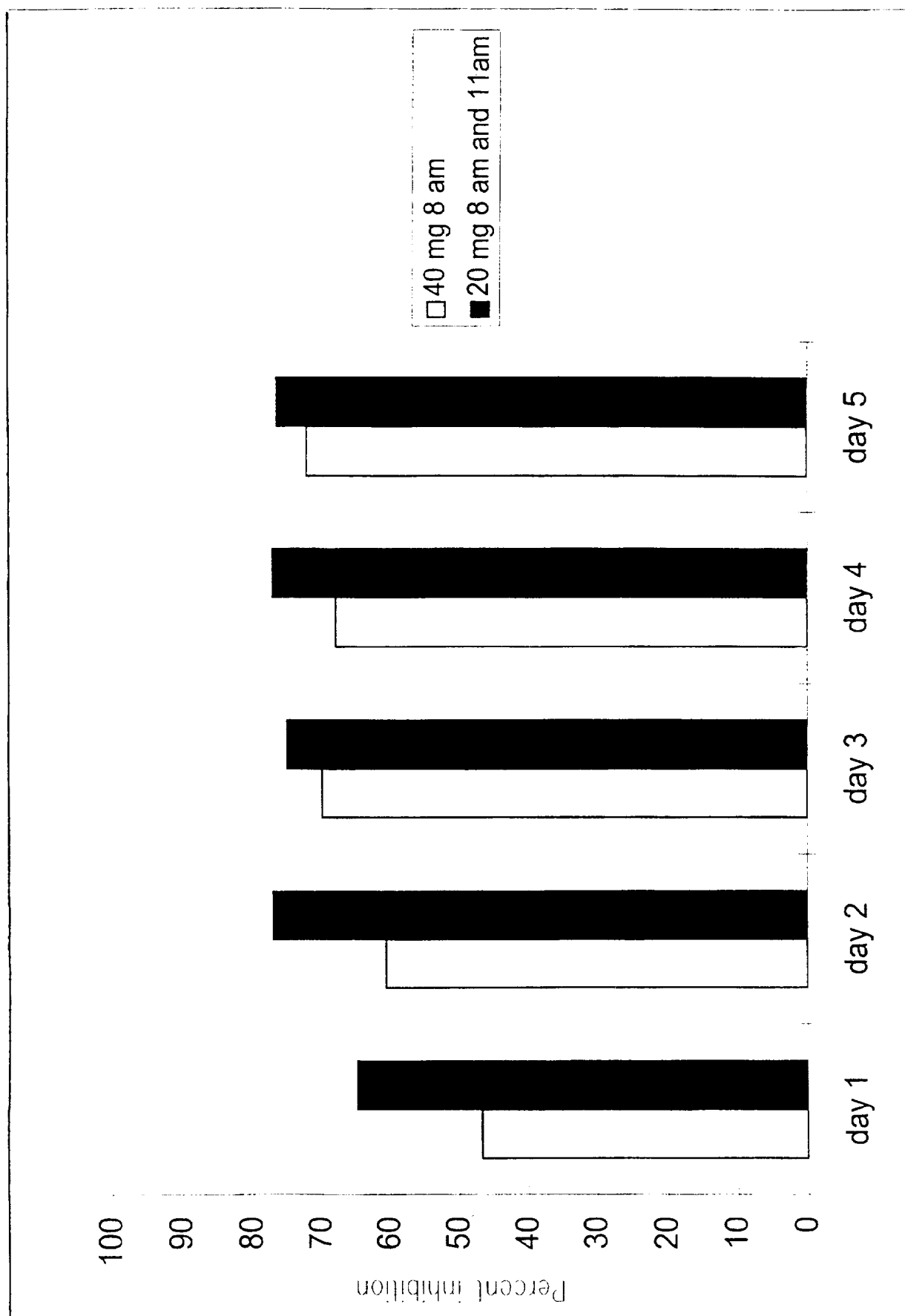


Figure 1.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01098

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/00, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96), page 15, line 16 - line 22  --	1-17
X	US 4853230 A (KURT I. LOVGREN ET AL), 1 August 1989 (01.08.89), column 10, line 51 - line 62  --	1-17
A	John E. Hoover "Remington's Pharmaceutical Sciences", 1975, Mack Publishing Company, Pennsylvania, page 702, column 1, line 43 - column 2, line 6  -----	1-17

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&amp;" document member of the same patent family

Date of the actual completion of the international search

17 October 1997

Date of mailing of the international search report

22 -10- 1997

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01098

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15-17  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Claims 15-17 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds and the compositions.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/97

International application No.

PCT/SE 97/01098

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		SU 1709894 A	30/01/92



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b>  <b>C07D 401/12</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/25711</b>  <b>(43) International Publication Date:</b> 27 May 1999 (27.05.99)
<b>(21) International Application Number:</b> PCT/SE98/01984  <b>(22) International Filing Date:</b> 3 November 1998 (03.11.98)  <b>(30) Priority Data:</b> 9704183-4 14 November 1997 (14.11.97) SE  <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> COTTON, Hanna [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). LARSSON, Magnus [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MATTSOON, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE).  <b>(74) Agent:</b> HÄLLGREN, Christer; Astra Aktiebolag, Intellectual Property, Patents, S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NEW PROCESS  <b>(57) Abstract</b>  <p>The present invention relates to a novel process for the synthesis of 5-methoxy-2- [[[4-methoxy-3, 5-dimethyl-2- pyridinyl)methyl] sulfinyl]-1H- benzimidazole, known under the generic name omeprazole. Moreover, the present invention also relates to manufacture of a pharmaceutical preparation thereof and its use in medicine. The novel process for the preparation of omeprazole, comprises the step of oxidizing 5-methoxy-2- [[[4-methoxy-3, 5-dimethyl-2- pyridinyl) methyl]thio]-1H- benzimidazole in an organic solvent with an oxidizing agent in the presence of a titanium complex and optionally in the presence of a base.</p>		

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<b>EE</b>	Estonia			<b>SG</b>	Singapore		

## NEW PROCESS

*Field of the invention*

5 The present invention relates to a novel process for the preparation of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. Moreover, the present invention also relates to the manufacture of a pharmaceutical preparation thereof and its use in medicine.

10 *Background of the invention and prior art*

The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more  
15 general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole and therapeutically acceptable salts thereof, are described in EP 5 129. This patent also discloses a process for the preparation of omeprazole and other structurally  
20 related substituted benzimidazoles.

US 5,386,032 describes an improved process for synthesis of omeprazole. This process describes the oxidation step and a work-up procedure for omeprazole. The oxidation step utilizes m-chloroperoxybenzoic acid in a solvent system consisting of an organic solvent  
25 and an aqueous phase of constant pH. The work-up procedure includes an extraction step and precipitation of omeprazole by the addition of an alkyl formate to the aqueous phase.

Another alternative process for the manufacture of omeprazole is described in US 5,391,752. This process utilizes magnesium monoperoxyphthalate as an oxidizing agent.

Omeprazole is a sulfoxide and a chiral compound, with the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the *R* and *S*-enantiomer of omeprazole. An enantioselective process for the synthesis of the single enantiomers of omeprazole is described in WO 96/02535. The asymmetric oxidation utilizes a chiral titanium complex to induce the chirality.

In the light of the above there was still a need for a new convenient and more efficient process for the manufacture of racemic omeprazole.

#### *Summary of the Invention*

The object of the present invention is to provide a novel process for the preparation of omeprazole. In the present invention, 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole is oxidized to omeprazole in an organic solvent with an oxidizing agent in the presence of a titanium complex, and optionally in the presence of a base. The present invention is further characterized in that omeprazole precipitates from the reaction mixture. Omeprazole, substantially free from titanium salts, can thereafter easily be filtered off from the reaction mixture and thereby avoiding time consuming steps, such as work up procedures including extraction. This precipitation of omeprazole from the reaction mixture is unexpected since the corresponding single enantiomers of omeprazole does not precipitate from the reaction mixture if the same reaction conditions are used.

This precipitation of omeprazole from the reaction mixture is advantageous and the present invention is the first process described for the preparation of omeprazole involving no extraction step. The precipitation of omeprazole results in a number of further advantages. Omeprazole is sensitive towards acid and over-oxidation, *i.e.* oxidation from sulfoxide to sulfone. However, since both these reactions take place in the solution phase, they are both suppressed by the fact that omeprazole precipitates from the reaction mixture. This

precipitation of omeprazole also suppresses other potential side-reactions, such as thermal decomposition of omeprazole.

The titanium complex suitable for catalysing the process of the present invention is prepared from a ligand and a titanium(IV) compound, preferably a titanium(IV)alkoxide, and optionally in the presence of additional water. An especially preferred titanium(IV)alkoxide is titanium(IV)isopropoxide or -propoxide. The amount of the titanium complex used in the present invention is not critical. An amount of less than approximately 0.50 equivalents, in proportion to the sulfide, is preferred and an especially preferred amount is 0.05 - 0.30 equivalents. However, less than 0.05 equivalents could also be used and the lower limit of 0.05 equivalents is only given for handling reasons.

The ligand used in the present invention to produce the titanium complex can be either an achiral or a chiral ligand of which the latter is preferred. Useful ligands are alcohols, such as diols, and preferably vicinal diols. The diol may be a branched or unbranched alkyl diol, or an aromatic diol. Preferred diols are esters of tartaric acid, such as ethyl esters.

The titanium complex may also be prepared by reacting titanium tetrachloride with a suitable ligand in the presence of a base.

The present invention is further characterized by that an achiral ligand or a mixture of stereoisomers, such as a mixture of enantiomers, of a chiral ligand is used. All mixtures including a racemic mixture is within the scope of the present invention.

In a preferred aspect of the present invention a racemic mixture of chiral ligands is used to prepare the titanium complex.

The oxidizing agent used is not crucial and can be selected to suit the reaction conditions and equipment used. Examples of such oxidizing agents include, but are not limited to, peroxyacides, such as m-chloroperoxybenzoic acid, and peroxides, such as cumene hydroperoxide, tert-butyl hydroperoxide and hydrogen peroxide. One advantage of the



present invention is that a less reactive and less corrosive oxidizing agent can be used to prepare omeprazole compared to those used in the prior art. The amount of oxidizing agent used according to the present invention is preferably approximately one equivalent, such as 0.9 to 1.05 equivalents, in proportion to the sulfide.

5

According to a preferred aspect of the invention, cumene hydroperoxide or tert-butyl hydroperoxide are used as oxidizing agent.

10

According to one aspect of the invention the oxidation is carried out in the presence of a base, such as 0.05 - 1.0 equivalents, preferably 0.15 - 0.3 equivalents. Optionally, the oxidation can be carried out in the absence of a base.

15

The base may be an inorganic or an organic base. Organic bases are preferred and especially suitable bases are amines, preferably triethylamine or N,N-diisopropylethylamine. The amount of base added to the reaction mixture is not crucial.

20

The oxidation is preferably carried out in an organic solvent around room temperature or above, *e.g.* between 10 - 60°C. Suitable organic solvents are for instance toluene, ethyl acetate, and the like. Toluene is the preferred solvent.

25

The order in which the reactants, *i.e.* the titanium compound, the ligand, the base, the solvent, water, and the 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]]thio]-1H-benzimidazole, are charged into the reaction vessel is not crucial and should be adapted to suit the equipment used. It is however preferred that all reactants are loaded into the reaction vessel before the oxidizing agent is added.

30

The preparation of the titanium complex may be performed at room temperature or at an elevated temperature and/or during a prolonged preparation time and in the presence or absence of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]]thio]-1H-benzimidazole.

According to one aspect of the present invention the titanium complex is prepared in the presence of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole.

An advantage of the process according to the present invention is that omeprazole precipitates from the reaction mixture without simultaneous precipitation of titanium salts. Due to this precipitation, omeprazole can be easily separated from the reaction mixture by filtration or centrifugation and thereby avoiding any time consuming work-up procedure.

The process of the present invention may also be used to produce not only omeprazole but also other substituted sulfinyl heterocyclic compounds known in the art, such as compounds with the generic names lansoprazole, pantoprazole, leminoprazole and rabeprazole.

The following example which will further illustrate the invention, but is not intended to limit the scope of the invention as defined hereinabove or as claimed below.

#### *Example*

5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.7 mmol) was dissolved in toluene (70 ml). The solution was heated to 50°C and water (0.030 ml) was added. To the resulting mixture was added diethyl(D,L)-tartrate (2.02 g, 9.78 mmol) in toluene (8 ml) and titanium(IV)isopropoxide (1.33 g, 4.68 mmol). The mixture was cooled to 30°C and diisopropylethylamine (0.962 g, 7.44 mmol) was added followed by cumene hydroperoxide (8.21 g, 53.9 mmol). The mixture was stirred at 30°C for 5h and the precipitated product was filtered off and washed with toluene (12 ml). Yield: 13.1 g (81%).

*CLAIMS*

1. A process for the preparation of omeprazole, comprising the step of oxidizing 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in an  
5 organic solvent with an oxidizing agent and optionally in the presence of a base characterized in that the oxidation is performed in the presence of a titanium complex.
2. A process according to claim 1, characterized in that the oxidation is performed in the presence of a base.
- 10 3. A process according to claim 1 or 2, characterized in that the titanium complex is prepared from a titanium(IV) compound and an enantiomeric mixture of chiral ligands.
4. A process according to claim 3, characterized in that the enantiomeric mixture is a  
15 racemic mixture.
5. A process according to claim 1, characterized in that the titanium complex is prepared from a titanium(IV) compound and an achiral ligand.
- 20 6. A process according to claim 1, characterized in that omeprazole precipitates from the reaction mixture.
7. A process according to claim 1, characterized in that no extraction step is used.
- 25 8. A process according to any of claims 1-7, characterized in that the titanium complex is prepared in the presence of 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole.

9. A process according to any of claims 1-8, characterized in that the oxidizing agent is cumene hydroperoxide or tert-butyl hydroperoxide.
10. A process according to any of claims 1-9, characterized in that the organic solvent is  
5       toluene.
11. A process according to any of claims 1-10, characterized in that the base is triethylamine or N,N-diisopropylethylamine.
- 10   12. A pharmaceutical formulation comprising omeprazole and a pharmaceutically acceptable carrier or diluent characterized in that the omeprazole is prepared according to any of claims 1-11.
13. Omeprazole prepared by a process according to any of claims 1-11.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01984

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9602535 A1 (ASTRA AKTIEBOLAG), 1 February 1996 (01.02.96)	1-2
A	--	3-11
X	EP 0005129 A1 (AKTIEBOLAGET HÄSSLE), 31 October 1979 (31.10.79)	12-13
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☐ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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**(54) Title:** STABLE DRUG FORM FOR ORAL ADMINISTRATION WITH BENZIMIDAZOLE DERIVATIVES AS ACTIVE INGREDIENT AND PROCESS FOR THE PREPARATION THEREOF

**(54) Bezeichnung:** STABILE ARZNEIFORM MIT BENZIMIDAZOLDERIVATEN ALS WIRKSTOFF ZUR ORALEN VERABREICHUNG UND VERFAHREN ZU IHRER HERSTELLUNG

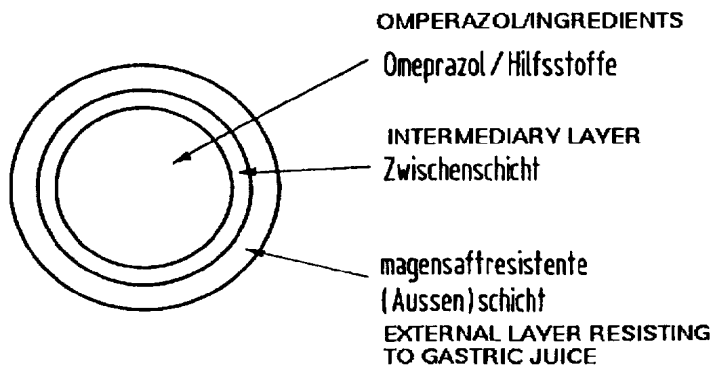
**(57) Abstract**

The invention relates to a stable drug form which is for oral administration and comprises: (a) a centre comprising an active ingredient selected from omeprazole, lansoprazole and pantoprazole, together with conventional auxiliary pharmaceutical ingredients, (b) an intermediate layer applied to the centre, and (c) an external layer which is resistant to gastric juice. The intermediate layer in (b) is in the form of a reactive layer comprising a polymeric layered material which is partly neutralised with alkalis, is resistant to gastric juice and has cation-exchange capacity. A process for the preparation of the stable drug form is also disclosed.

**(57) Zusammenfassung**

Die Erfindung betrifft eine stabile Arzneiform zur oralen Verabreichung, welche (a) einen Kern, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit üblichen pharmazeutischen Hilfsstoffen, (b) eine auf den Kern aufgetragene Zwischenschicht, und (c) eine magensaftresistente Außenschicht umfaßt. Die Zwischenschicht in (b) ist als reaktive Schicht ausgebildet, in der ein mit Alkalien teilneutralisiertes magensaftresistentes Polymer-Schichtmaterial mit Kationenaustauscherkapazität vorliegt. Ferner wird ein Verfahren zur Herstellung der stabilen Arzneiform offenbart.

**Schematischer Schichtaufbau gemäß der Erfindung**  
**FIGURE SHOWING THE STRUCTURE OF LAYERS ACCORDING TO THE INVENTION**



# **LEDIGLICH ZUR INFORMATION**

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## Stabile Arzneiform mit Benzimidazolderivaten als Wirkstoff zur oralen Verabreichung und Verfahren zur ihrer Herstellung

Die vorliegende Erfindung offenbart eine stabile Arzneiform zur oralen Verabreichung, welche als Wirkstoff eines oder mehrere der Benzimidazolderivate Omeprazol, Lansoprazol oder Pantoprazol enthält, sowie ein Verfahren zu ihrer Herstellung.

Aus EP 0 005 129 ist bekannt, daß Omeprazol (5-Methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridyl)methyl)sulfinyl)-1H-benzimidazol) als ein potenter Inhibitor bei der Sekretion von Magensäure fungiert. Omeprazol hat sich in der Therapie von Ulcus duodeni, Ulcus ventriculi, Refluxösophagitis und Zollinger-Ellision-Syndrom bewährt. Dabei kommen parenterale und feste perorale Arzneimittel zur Anwendung.

Die folgenden für Omeprazol gemachten Ausführungen gelten in gleicher Weise für Lansoprazol (2-(((3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridyl)methyl)sulfinyl)-1H-benzimidazol) und Pantoprazol (5-Difluormethoxy-2-((3,4-dimethoxy-2-pyridyl)methylsulfinyl)-1H-benzimidazol).

Die Verabreichung eines Arzneimittels per os ist besonders bequem, da sie ohne Aufwand und unangenehme Begleiterscheinungen vom Patienten selbst praktisch überall und zu jeder Zeit durchgeführt werden kann. Der orale Verabreichungsweg bringt es zwangsläufig mit sich, daß das Arzneimittel zunächst in den Magen gelangt. Omeprazol und dessen Derivate degradieren jedoch sehr schnell im sauren Milieu des Magens zu unwirksamen Verbindungen. In wässriger Lösung hat Omeprazol beispielsweise bei pH-Werten von unter 4 eine Halbwertszeit von weniger als 10 Minuten. Feste perorale Arzneiformen (Tabletten, Pellets, Granulate) von Omeprazol und ähnlichen Wirkstoffen müssen deshalb vollständig gegen Magensaft geschützt werden.

Die Resorption von Omeprazol erfolgt im oberen Duodenum, wobei dieser Wirkstoff einen ausgeprägten First-Pass-Effekt zeigt.

Es muß daher eine möglichst rasche und vollständige Freisetzung des Wirkstoffes aus der Arzneiform nach Passage des Pylorus sichergestellt werden, um ausreichend hohe Bioverfügbarkeit zu gewährleisten.

Omeprazol wird hierzu mit einem Überzug aus enterischen, d.h. magensaftresistenten Materialien versehen, der einerseits im sauren Milieu des Magens (ca. pH 1 bis 3) unlöslich ist, sich aber andererseits im schwach sauren bis schwach alkalischen Bereich des Duodenums (pH >5,5) auflöst. Bekannt ist, die extrem säureempfindliche Wirksubstanz Omeprazol in den Kern einer Pelletformulierung einzubringen, auf welcher eine oder mehrere Überzugsschichten vorgesehen sind.

Als Schichtmaterial wird häufig Eudragit® L100 oder L100-55 benutzt. Eudragit® L100 ist ein Copolymer aus Methacrylsäure und Methylmethacrylat in einem bestimmten Verhältnis und ist in saurem Milieu, z.B. im Magen, unlöslich und bildet somit eine weitgehend undurchlässige Schutzschicht aus. Eudragit® L100-55 ist ein Copolymer aus Methacrylsäure und Ethylacrylat, wobei das Verhältnis der Monomeren so ausgewählt ist, daß es bei einem pH <5,5 unlöslich, bei einem pH darüber aber löslich ist. Der Grund dafür liegt im wesentlichen darin, daß die Carboxylseitengruppen des Polymers im sauren Milieu protoniert vorliegen, und das Polymer damit insgesamt ungeladen ist. Im schwach sauren, neutralen bzw. basischen Milieu, z.B. im Darmbereich, deprotonieren die Carboxylgruppen, wodurch das Polymer negative Ladungen erhält. Es wird wasserlöslich, wobei der Wirkstoff freigesetzt wird.

Eudragit kann jedoch nicht direkt auf den Omeprazol-Kern aufgebracht werden, da die Carboxylgruppen in der Überzugsschicht das Omeprazol degradieren, was auch Probleme bei der Herstellung und bei der Lagerung der Arzneiform mit sich bringt. Schon geringe Mengen an Degradationsprodukten führen zu deutlichen Farbveränderungen und damit Qualitätseinbußen, die unter Umständen keine Verabreichung am Patienten mehr erlauben. Die Lagerungsprobleme werden

verschärft, wenn durch Haarrisse und andere Defekte in der Überzugsschicht Feuchtigkeit in den wirkstoffhaltigen Kern eindringt.

Für den Schutz fester peroraler Arzneimittel mit Omeprazol, Lansoprazol oder Pantoprazol als Wirkstoff vor ungünstigen Lagerungsbedingungen und bei der oralen Einnahme vor dem Magensaft eignen sich magensaftresistente Überzüge aus den obengenannten Polymeren, die durch eine inerte Isolierschicht vom wirkstoffhaltigen Kern getrennt werden. Darüber hinaus hat es sich als sinnvoll erwiesen, den wirkstoffhaltigen Kern durch Zusatz einer alkalisch reagierenden Substanz zu stabilisieren. Andererseits muß eine ausreichend schnelle Freisetzung im Darm sichergestellt sein.

#### **Stand der Technik**

DE 1 204 363 beschreibt eine Arzneiform bestehend aus einem Kern mit drei darauf aufgebracht, unterschiedlichen Schichten. Die erste (innerste) Schicht ist im Magen löslich, im Darm aber unlöslich. Die zweite Schutzschicht ist wasserlöslich (unabhängig vom pH-Wert) und die dritte (äußere) Schutzschicht ist ein magensaftresistenter Überzug. Für Omeprazol ist diese Formulierung jedoch nicht geeignet, weil sie sich nur langsam im Darm auflöst. Eine schnelle Auflösung im Darm ist jedoch für die angestrebte Bioverfügbarkeit wesentlich.

EP 0 247 983 offenbart ein pharmazeutisches Mittel zur oralen Verabreichung, das Omeprazol als wirksamen Bestandteil umfaßt. Das Kernmaterial enthält Omeprazol zusammen mit einer alkalisch reagierenden Verbindung oder einem Omeprazol-Salz, gegebenenfalls zusammen mit einem alkalisch reagierenden Hilfsstoff. Zwischenschichten, die eine Trennschicht zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht aus einem magensaftresistenten Überzug bilden, umfassen wasserlösliche oder darin rasch zerfallende Tablettenträgermittel oder polymere, wasserlösliche,

filmbildende Substanzgemische, die gegebenenfalls puffernde, alkalische Verbindungen enthalten und von außen eindringende Protonen abfangen sollen. Abgesehen von seiner Wasserlöslichkeit ist das Schichtmaterial chemisch und physikalisch inert.

Allerdings kann bei Verwendung einer alkalisch puffernden Substanz, wie z.B. Natriumacetat, diese in der Zwischenschicht frei diffundieren und in die äußere magensaftresistente Schicht eindringen. Die damit einhergehende Erhöhung des pH-Wertes kann das Vordringen von Feuchtigkeit durch die enterische Schicht aufgrund der zunehmenden Löslichkeit begünstigen. Dies bedeutet, daß bei Eindringen höherer Konzentrationen von Protonen die Gefahr besteht, daß diese in den Kern gelangen, und dort das Omeprazol zerstören. Letzteres kann insbesondere dann leicht eintreten, wenn die äußere magensaftresistente Schicht aufgrund von Imperfektionen, wie sie sich bei der Herstellung ergeben können, physikalischer Belastung oder durch Alterungserscheinungen bei der Lagerung Risse und Sprünge aufweist.

EP 0 519 144 beschreibt Omeprazol-Pellets bestehend aus einem inerten Pelletkern, der mit dem mikronisierten Wirkstoff beschichtet ist und anschließend mit einer magensaftresistenten Schicht überzogen wird. Zur Beschichtung des Kerns mit Omeprazol werden folgende Hilfsstoffe, dispergiert in Wasser, eingesetzt: Hydroxymethylcellulose (HMC), wasserfreie Lactose, L-Hydroxypropylcellulose (L-HPC), Natriumlaurylsulfat, Dinatriumhydrogenphosphatdihydrat. Als magensaftresistenter Überzug wird Hydroxypropylmethylcellulose-phthalat (HPMCP) verwendet. Bei dieser Vorgehensweise ist eine mögliche Reaktion des Omeprazol mit dem Polymer nicht ausgeschlossen, was insbesondere zu einer verschlechterten Lagerungsstabilität führen kann.

EP 0 496 437 umfaßt Pelletkerne bzw. Tabletten, die Omeprazol oder ein Alkalisalz von Omeprazol zusammen mit einer alkalisch reagierenden Verbindung (Puffer) enthalten und mit einer

Schicht wasserlöslicher, filmbildender Hilfstoffe, die bevorzugt alkalisch reagieren (Puffer), sowie mit einem magensaftresistenten äußeren Film überzogen sind.

EP 0 239 200 verwendet basische Magnesiumsalze und/oder basische Calciumsalze zur Stabilisierung von Benzimidazol-Derivaten mit Omeprazol als einen typischen Vertreter.

Es wurden demnach zahlreiche Bemühungen zur Herstellung von Omeprazol-Arzneiformen unternommen, die die Verfärbung des Wirkstoffes verhindern, den chemischen Abbau von Omeprazol weitgehend reduzieren, die Degradation des Wirkstoffes im sauren Magensaft unterbinden, aber gleichzeitig im Milieu des Dünndarms den Wirkstoff möglichst rasch freigeben sollen.

Aufgabe der vorliegenden Erfindung ist es, eine zur oralen Verabreichung geeignete, gegenüber dem Stand der Technik verbesserte Arzneiform zur Verfügung zu stellen, die als Wirkstoff Omeprazol, Lansoprazol und/oder Pantoprazol, gegebenenfalls in Kombination mit weiteren pharmazeutisch wirksamen Substanzen, enthält, und bei ausgedehnter Lagerung und unter chemisch-physikalischer Belastung eine ausgezeichnete Stabilität besitzt. Insbesondere soll mit der erfindungsgemäßen Arzneiform das Eindringen von saurem Magensaft an Sprüngen, Rissen, Kanten oder jeglichen anderen Imperfektionen der Überzugsschicht in die Kernschicht vermieden und dadurch ein Abbau der säurelabilen Wirkstoffe verhindert werden.

Die erfindungsgemäße Arzneiform gewährleistet eine sehr hohe Arzneimittelsicherheit, die vor allem auch dann gegeben sein soll, wenn sich im Verlauf des Herstellungsverfahrens der Arzneiform sowie bei der Handhabung derselben bzw. deren Verpackungsform durch den Patienten ungünstige Bedingungen ergeben.

Gleichzeitig ist es erforderlich, daß die Arzneiform nach Passage durch den Magen den Wirkstoff im Dünndarm rasch

freisetzt. Ferner soll der Arzneiaufbau das Auftreten von Verfärbungen des Wirkstoffes verhindern.

Die vorstehende Aufgabe wird erfindungsgemäß gelöst durch eine stabile Arzneiform zur oralen Verabreichung, welche

- (a) einen Kern, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit üblichen pharmazeutischen Hilfsstoffen enthält,
- (b) eine auf den Kern aufgebrachte Zwischenschicht, und
- (c) eine magensaftresistente Außenschicht umfaßt, und die sich dadurch auszeichnet, daß in (b) eine reaktive Zwischenschicht aus einem mit Alkalien teilneutralisierten magensaftresistenten Polymer-Schichtmaterial mit Kationenaustauscherkapazität vorliegt.

Gegenstand der Erfindung ist ferner ein Verfahren zur Herstellung der vorstehend genannten Arzneiform, wonach man

- (a) als Kern Formling bildet, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit üblichen pharmazeutischen Hilfsstoffen enthält,
- (b) auf den Formling eine Zwischenschicht aufbringt, und
- (c) den überzogenen Formling mit einer magensaftresistenten Schicht befilmt,

und das Verfahren dadurch gekennzeichnet ist, daß man in (b) eine reaktive Zwischenschicht aus einem mit Alkalien teilneutralisierten magensaftresistenten Polymer-Schichtmaterial mit Kationenaustauscherkapazität aufbringt.

Bevorzugte Ausführungsformen der Erfindung sind in den abhängigen Ansprüchen wiedergegeben.

Der Schichtaufbau der erfindungsgemäßen Arzneiform ist schematisch in Abbildung 1 wiedergegeben.

Der Kern der erfindungsgemäßen Arzneiform umfaßt den Wirkstoff Omeprazol, Lansoprazol oder Pantoprazol einzeln oder Kombinationen davon zusammen mit üblichen Hilfssubstanzen. Für die Stabilität der erfindungsgemäßen Arzneiform ist es nicht



erforderlich und auch nicht bevorzugt, daß der Kern aus dem Wirkstoff zusammen mit einer alkalisch reagierenden Verbindung formuliert wird. Es ist auch nicht notwendig, daß ein alkalisches Salz des Wirkstoffes eingesetzt wird.

Als pharmazeutische Hilfsstoffe für den Kern eignen sich insbesondere Füllstoffe, wie Mannit, Hydroxypropylcellulose, mikrokristalline Cellulose und wasserfreie Lactose. Darüber hinaus hat sich gezeigt, daß bei Verwendung einer speziellen Kombination von Mannit und Hydroxypropylcellulose als nicht alkalisierende Hilfsstoffe im Kern vorteilhafte Stabilitätseffekte erzielt werden können.

Der Kern kann auch Netzmittel umfassen, die in geeigneter Weise ausgewählt sind aus Natriumlaurylsulfat, Sorbitanfettsäureester und Polyoxyethylensorbitan-Fettsäureester.

Der Kern der erfindungsgemäßen Arzneiform kann als Formling ausgebildet sein. Bevorzugte Formlinge sind Pelletkerne, Tabletten, Mikrotabletten oder Granulate.

Die Formlinge sind mit einer Zwischenschicht überzogen. Diese Zwischenschicht weist bevorzugt eine Schichtdicke von etwa 5 bis 30  $\mu\text{m}$  auf. Sie bildet sowohl eine mechanische als auch chemische Barriere zum Kern hin. Dabei ist es erforderlich, daß diese Zwischenschicht als intakter Film vorliegt. Das Polymer der Zwischenschicht macht etwa 3 bis 5 Gew.-% des Kerngewichts aus.

Die Zwischenschicht umfaßt ein magensaftresistentes Polymer-Schichtmaterial, das mit Alkalien auf einen pH-Bereich von 5,5 bis 7,0, bevorzugt 5,5 bis 6,5 eingestellt wurde. Bei diesen pH-Werten sind noch nicht alle Protonen der Säurefunktionen des Polymermaterials ausgetauscht, das Material ist lediglich teilneutralisiert. Wie aus Abbildung 2 hervorgeht, liegen im Falle von Eudragit bei einem pH von 5,5 weniger als 40 % der Carboxylfunktionen neutralisiert vor. Trotzdem ist eine

Kombination von auf pH 5,5 teilneutralisiertem Eudragit mit Omeprazol unerwartet auch unter verschärften Lagerungsbedingungen noch stabil (siehe Beispiel 2). Bei pH 7,0 sind ca. 97 % der Carboxylfunktionen des Eudragits neutralisiert (siehe Abbildung 2).

Unter Alkalien versteht man Substanzen, deren Lösung mit Wasser alkalische Reaktionen zeigen (Römpps Chemie Lexikon, 8.Auflage, 1979). In erster Linie gehören hierzu die Hydroxide der Alkalimetalle, insbesondere Natrium und Kalium, aber auch die Hydroxide der Erdalkalimetalle. Erfindungsgemäß bevorzugt sind die Hydroxide der Alkalimetalle, insbesondere Natriumhydroxid.

Bei der Teilneutralisierung werden die Protonen der an den Polymerketten des Schichtmaterials anhängenden Säurefunktionen, z.B. Carboxylgruppen, teilweise durch z.B. Alkalimetallionen als Gegenionen ersetzt. Das derart modifizierte Polymer-Schichtmaterial ist in Gegenwart von Protonen nicht mehr physikalisch-chemisch inert, sondern reaktiv, da es nunmehr Kationenaustauscherkapazität besitzt. Dies bedeutet, daß bei Eindringen von Feuchtigkeit und insbesondere saurem Magensaft an Rissen, Spalten, Kanten oder anderen Imperfektionen durch die äußere Schicht der erfindungsgemäßen Arzneiform die eindringenden Protonen abgefangen und durch unschädliche Alkalimetallionen ausgetauscht werden. Ein weiterer Aspekt des reaktiven Prinzips des Zwischenschichtmaterials zeigt sich darin, daß sich die Zwischenschicht an diesen Stellen zu einer magensaftresistenten Barriere umwandelt, sie besitzt gewissermaßen einen "Self-Repair-Mechanismus". Praktische Versuche haben gezeigt, daß sich bei Kontakt der Zwischenschicht mit einem sauren Medium eine gelartige Substanz ausbildet, welche nicht nur Protonen abfängt, sondern auch eine flexible mechanische Barriere ausbildet, die das weitere Eindringen von Feuchtigkeit bzw. saurem Medium verhindert. Die Teilneutralisierung des Polymermaterials für die reaktive Zwischenschicht auf einen pH-Bereich von 5,5 bis

6,5 ist insbesondere deswegen bevorzugt, weil sich bereits eine magensaftresistente Barriere ausbildet, wenn nur wenige Protonen durch die äußere Schicht eindringen, andererseits der Omeprazolkern noch ausreichend stabil ist.

Hierdurch wird auch ein deutlich verbessertes Stabilitätsverhalten der beanspruchten Arzneiform bei ausgedehnter Lagerung und unter chemisch-physikalischer Belastung erreicht.

Puffernde bzw. alkalisierende Zusätze in der Zwischenschicht, wie z.B. in EP 0 247 983 vorgeschlagen, sind nicht mehr notwendig und können vielmehr schädlich sein, da sie die Löslichkeit der Zwischenschicht erhöhen und damit deren Schutzfunktion mindern. Dies läuft dem erfindungsgemäßen "Self-Repair-Mechanismus" geradezu entgegen; je mehr basische Äquivalente in der Zwischenschicht vorhanden sind, desto mehr Protonen müssen von außen eindringen, damit der "Self-Repair-Mechanismus" der reaktiven Schicht schnell zum Tragen kommt.

Als bevorzugte Substanzen für die Zwischenschicht eignen sich die von Röhm Pharma, Deutschland, hergestellten Polymermaterialien Eudragit® L100-55, Eudragit® L100, sowie Hydroxypropylmethylcellulosephthalat (HPMCP) und Celluloseacetatphthalat (CAP), die, wie oben beschrieben, vor der Anwendung als Zwischenschicht, also vor dem Aufsprühen derselben, mit Alkalien teilneutralisiert werden. Besonders bevorzugt ist das als kommerzielles Handelsprodukt weltweit erhältliche Eudragit® L100-55.

Die Zwischenschicht kann übliche Zusätze, z.B. einen Weichmacher enthalten. Bevorzugt eignen sich hierfür Triethylcitrat, Acetyltriethylcitrat, acetylierte Monoglyceride, Propylenglykol, Polyethylenglykole.

Die überzogenen Formlinge, d.h. der Kern und die Zwischenschicht, werden dann zur Herstellung der erfindungsgemäßen Arzneiform mit einer Außenschicht überzogen.

Diese Außenschicht stellt eine übliche enterische, magensaftresistente Schicht dar. Als Materialien eignen sich hierfür handelsübliche, wässrige Polymerdispersionen, wie Polymethacrylate, z.B. Eudragit® L100-55 (Röhm Pharma), und Coating CE 5142 (BASF). Außerdem können zur Bildung der magensaftresistenten Schicht auch Polymere verwendet werden, die in organischen Lösungsmitteln löslich sind. Als geeignete Stoffe sind z.B. Phthalate (Celluloseacetatphthalat, Hydroxypropylmethyl-cellulosephthalat) zu nennen. Außerdem kann die Außenschicht der erfindungsgemäßen Arzneiform Antihaftmittel, Dispergierungsmittel, Pigmente und Farbstoffe enthalten. Ein geeignetes Antihaftmittel ist beispielsweise Talkum.

Es wurde überraschenderweise festgestellt, daß die erfindungsgemäße Kombination aus enterischer äußerer Schicht und reaktiver Zwischenschicht gegenüber konventionellen Arzneimittelformen mit inerter Zwischenschicht ein beschleunigtes Auflösungsverhalten im künstlichen Darmsaft (pH ca. 5,8) zeigt. Dieser Effekt läßt nicht nur eine sehr rasche Freisetzung des Wirkstoffes im schwach sauren bis schwach alkalischen Milieu des Dünndarms und damit eine ausgezeichnete Bioverfügbarkeit erwarten, sondern ermöglicht auch eine verbesserte Arzneimittelsicherheit, da die enterische Außenschicht verstärkt werden kann, ohne daß eine gewünschte rasche Freisetzung verzögert wird. Hierdurch kann nicht nur die Magensaftresistenz, sondern auch die Arzneimittelstabilität, insbesondere bei ungünstigen Lagerungsbedingungen, weiter verbessert werden. Die Dicke der magensaftresistenten Außenschicht der erfindungsgemäßen Arzneiform beträgt daher 20 bis 60 µm (ca. 10 bis 50 Gew.-% bezogen auf den Kern), bevorzugt 30 bis 60 µm.

In einer vorteilhaften Ausführungsform der Erfindung besteht die reaktive Zwischenschicht aus auf einen pH-Wert von 5,5 bis 7,0, bevorzugt 5,5 bis 6,5, teilneutralisiertem Eudragit® L100-55, und die äußere Schicht aus handelsüblichem Eudragit® L100-55 (pH ca. 2 bis 3). Der pH-Übergang zwischen äußerer

Schicht und Zwischenschicht muß nicht unbedingt sprunghaft sein, sondern kann auch als Gradient ausgebildet sein. Dies kann erreicht werden, wenn von innen nach außen mehrere dünne Eudragit-Schichten aufgebracht werden, die jeweils auf einen abnehmenden pH-Wert teilneutralisiert wurden.

Sowohl die reaktive Zwischenschicht als auch die magensaftresistente Außenschicht kann als Vielzahl von Einzelschichten ausgebildet sein.

Die vorliegende Erfindung umfaßt ferner ein Verfahren zur Herstellung einer stabilen Arzneiform zur oralen Verabreichung, welche Omeprazol, Lansoprazol und/oder Pantoprazol als Wirkstoff enthält.

Gemäß dem erfindungsgemäßen Verfahren werden der Wirkstoff und Hilfsstoffe, wie Mannit, Hydroxypropylcellulose und Natriumlaurylsulfat zusammen mit einem geeigneten Lösungsmittel, bevorzugt Isopropanol, angefeuchtet, granuliert und zu den gewünschten Formlingen (z.B. Pellets, Granulat, Tabletten) nach üblichen Verfahren verarbeitet. Die Formlinge werden anschließend mit einer wässrigen Dispersion, bestehend aus einer mit Alkalien auf einen pH-Wert von ca. 5,5 bis ca. 7,0 teilneutralisierten magensaftresistenten Substanz, bevorzugt Eudragit® L100-55, sowie einem Antihaftmittel und/oder Weichmacher, wie Talkum und Triethylcitrat, z.B. in einer Wirbelschichtapparatur unter Bildung der Zwischenschicht mit Kationenaustauscheraktivität befilmt. Eine dem Eudragit® L100-55 entsprechende Qualität ist auch als fertige Suspension unter der Bezeichnung Eudragit® L30D-55 im Handel erhältlich. Im Anschluß daran erfolgt die Beschichtung mit einer magensaftresistenten Substanz (z.B. Eudragit® L100-55), Talkum und einem Weichmacher (wie z.B. Triethylcitrat) zur Ausbildung der enterischen Außenschicht der erfindungsgemäßen Arzneiform.

Bevorzugt ist die Herstellung von Pellets, die in einer für eine gewünschte Wirkstoffdosis genügenden Menge in Gelatine kapseln gefüllt werden.

Die so hergestellte Kapselformulierung kann neben den die genannten Benzimidazolverbindungen enthaltenden Pellets noch andere Wirkstoffe enthalten. Bevorzugt ist eine Kombination von Diclofenac- und Omeprazol-haltigen Pellets. Die Diclofenac-haltigen Pellets sind bevorzugt nach dem erfindungsgemäßen Verfahren hergestellt, d.h. sie enthalten ebenfalls eine reaktive Zwischenschicht. Sie können aber auch nach bekannten Verfahren, wie z.B. in EP 0 348 808 offenbart, hergestellt werden. In einer weiteren Ausführungsform liegen die Diclofenac-haltigen Pellets als Mischung magensaftresistent umhüllter Pellets und retardiert durchlässiger Pellets vor, die erst in tieferen Darmabschnitten freigesetzt werden.

Kombinationen von nicht-steroidalen Entzündungshemmern und Schmerzmitteln sind an sich bekannt. So nennt EP 0 527 887 beispielsweise die Kombination von Diclofenac (o-(2,6-Dichloranilino)phenylelessigsäure), einem hochwirksamen NSAID (Non-Steroidal-Anti-Inflammatory-Drug), mit Misoprostol, die unter der Marke Arthrotec®, Heumann Pharma GmbH, Deutschland, zur Behandlung von schmerzhaften Entzündungserkrankungen eingesetzt wird. Das Prostaglandin-Derivat Misoprostol dient hierbei zur Prävention von NSAID-assoziierten Ulcuserkrankungen.

Die feste Kombination von Diclofenac und Omeprazol hat bei der Langzeitbehandlung von Schmerz/Entzündungen eine Reihe von Vorteilen. So hält eine Kombination von Diclofenac mit Omeprazol die Ulcusrate bei Patienten, die ein hohes Risiko für die Entstehung gastrointestinaler Ulzera aufweisen und die gleichzeitig der Behandlung mit einem NSAID bedürfen, niedrig (Ulcus-Prävention). Ferner erzielt diese Kombination hohe Ulcus-Abheilraten in Verbindung mit ausreichender Schmerzlinderung (Therapie). Aufgrund der guten Wirksamkeit und der guten Verträglichkeit der Kombinationspartner in Verbindung mit einer Verabreichung von nur einmal täglich läßt sich die Patienten-Compliance erheblich steigern.

Die zur unmittelbaren Verabreichung *per os* geeignete Kapselformulierung enthält als Einheitsdosis 25 bis 200 mg, vorzugsweise 75 bis 150 mg Diclofenac und 10 bis 40 mg, vorzugsweise 10 oder 20 mg Omeprazol in erfindungsgemäßen Pellets.

Die Vorteile der erfindungsgemäßen Arzneiform gegenüber Omeprazol- und anderen Benzimidazol-haltigen Arzneiformen des Standes der Technik bestehen insbesondere darin, daß an Imperfektionen der Außenschicht, an denen bei Lagerung Feuchtigkeit oder nach peroraler Verabreichung saurer Magensaft in die Kernschicht vorzudringen vermag, die reaktive Zwischenschicht die Protonen nicht nur abfängt, sondern darüber hinaus in ein magensaftresistentes Schichtmaterial zurückverwandelt wird. Durch diesen "Self-Repair-Mechanismus" bildet sich eine gelartige Schicht aus, die das Eindringen von Feuchtigkeit und Säure in den Kern der Arzneiform zu verhindern vermag. Für den Fall, daß kein Magensaft eindringt, bleibt diese Zwischenschicht löslich. Unerwarteterweise zeigt die Kombination aus enterischer Außenschicht und reaktiver Zwischenschicht darüber hinaus ein verbessertes Auflösungsverhalten im künstlichen Darmsaft, was auf ein entsprechend gutes Auflösungsverhalten im Dünndarm schließen läßt.

Die Erfindung wird anhand der nachfolgenden Beispiele näher erläutert, ohne diese dadurch zu beschränken.

Beispiel 1

In vitro Versuche zur chemisch/physikalischen Stabilität der erfindungsgemäßen Arzneiform: Verreibungen von Omeprazol und Zwischenschichtmaterial

Es wurden Lagerungsversuche mit Verreibungen von Omeprazol und verschieden behandelten Zwischenschichtmaterialien über 32 Tage bei 40°C und 75% relativer Feuchte (rF) durchgeführt. Anschließend wurde mit HPLC untersucht, in welchem Maße der Wirkstoff Omeprazol (Restgehalt in Gew.-%) stabil blieb, zu welchem Prozentsatz Degradationsprodukt entstanden (Flächen-% aus Reinheitschromatogramm) und in welchem Maße sich Verfärbungen einstellten. Dabei wurde Omeprazol mit einem nicht vorbehandelten, zur Ausbildung von magensaftresistenten Überzügen verwendeten enterischen Schichtmaterial (HPMCP, Charge 1 a, und Eudragit® L100-55, Charge 1 b, pH 2-3) und mit erfindungsgemäß vorbehandeltem enterischen Schichtmaterial (Eudragit® L100-55) verrieben und offen unter den angegebenen Bedingungen in Petrischalen gelagert. Das vorbehandelte Eudragit® L100-55 war zuvor mit Natriumhydroxid auf pH 5,5 (Charge 1 c) und pH 7,0 (Charge 1 d) teilneutralisiert worden.

Die Ergebnisse sind in Tabelle 1 wiedergegeben. Die angegebenen Werte entsprechen dem Mittel von zwei Probenaufbereitungen. Die Verfärbungen sind als Farbwerte nach dem "Taschenlexikon der Farben", A.Kornerup und J.H.Wauscher, Muster-Schmidt-Verlag, Zürich, Göttingen, 3.Aufl, 1981, wiedergegeben.



Tabelle 1

Charge	Verreibung Omeprazol + ..... (1:1)	Gehalt Omeprazol Gewichtsprozent-[%]		Degradationsprodukt Flächen-[%]		Farbwert (Standard - Farbtafel)		
		nach Herstellung	nach 32 Tagen	nach Herstellung	nach 32 Tagen	nach Herstellung	nach 32 Tagen	
Referenzbeispiel								
1 a	HPMCP	100	⇔	85	< 0,1	⇔	5A1-2 (weiß - schwach- orange)	7C5 (braun)
1 b	Eudragit L 100-55 pH 2-3	100	⇔	97	< 0,1	⇔	4A2 (schwach - hellgelb)	6B4 (braun-orange)
erfindungsgemäß								
1 c	Eudragit L 100-55 pH 5,5	100	⇔	97	< 0,1	⇔	1A1-2 (weiß - schwach hellgelb)	12B2 (schwach-hellgrau)
1 d	Eudragit L 100-55 pH 7,0	100	⇔	98	< 0,1	⇔	1A1-2 (weiß - schwach hellgelb)	11C2 (schwach hellgrau)

Aus der Spalte "Gehalt Omeprazol" ist zu entnehmen, daß bei Verwendung von teilneutralisiertem magensaftresistenten Polymermaterial gemäß der Erfindung der Wirkstoff wesentlich stabiler bleibt als in einer Verreibung mit einer üblichen enterischen Substanz, die zu 100% freie Carboxylgruppen besitzt. So werden nach 32 Tagen Lagerung unter den genannten Bedingungen erfindungsgemäß nur 2 bzw. 3% des Wirkstoffes Omeprazol abgebaut. Dagegen ist bei Verwendung des im Stand der Technik üblichen enterischen Schichtmaterials HPMCP bei den vorliegenden Verreibungsversuchen nach 32 Tagen ein Omeprazolabbau bis zu 15 Gew.-% festzustellen. Allerdings zeigt sich auch bei Einsatz von nicht neutralisiertem Eudragit noch kein deutlicher Omeprazolabbau (3 Gew.-%).

Dafür ergeben sich beim Vergleich des Gehaltes eines im HPLC-Chromatogramm auftretenden Omeprazol-Degradationsproduktes bei Verwendung von erfindungsgemäßigem teilneutralisiertem Eudragit (pH 5.5 und 7.0) mit handelsüblichem Eudragit (pH 2 bis 3) deutliche Unterschiede (siehe Spalte "Degradationsprodukt"). So wird gemäß der Erfindung nach 32 Tagen kaum Degradationsprodukt (0,25 Flächen-% in beiden Chargen) festgestellt, während in Gegenwart von handelsüblichem Eudragit (pH 2 bis 3) ca. 0,99 Flächen-%, und in Gegenwart eines üblichen Schichtmaterials (HPMCP) sogar ca. 7% Degradationsprodukt vorliegen. Dieses Ergebnis wird durch den Farbvergleich bestätigt (siehe Spalte "Farbwert"). Weder das braune Produkt der Charge 1 a noch das braun-orange Produkt der Charge 1 b sind verkaufsfähig. Das erfindungsgemäß behandelten Produkte (Chargen 1 c und d) zeigen dagegen eine wesentlich geringere Farbveränderung.

Die vorstehenden Versuche belegen, daß in Gegenwart von hoher Feuchte und erhöhter Temperatur (verschärfter Stabilitätstest) das erfindungsgemäß teilneutralisierte Schichtmaterial auch im verriebenen Zustand schützend auf den Wirkstoff Omeprazol wirkt. Dagegen zeigt übliches enterisches Schichtmaterial, welches zu 100% freie COOH-Gruppen aufweist,

nicht nur keine solche Schutzwirkung, sondern verursacht eine deutliche Degradation des Wirkstoffs.

### Beispiel 2

#### Stabilität von Pelletformulierungen

In einer weiteren Versuchsreihe wurde die Arzneiform gemäß der Erfindung mit der des Standes der Technik (EP 0 247 983) verglichen. Hierzu wurden verschiedene Pelletchargen hergestellt, die einen dreischichtigen Aufbau zeigen:

- Kern, mit dem Wirkstoff Omeprazol, einmal in Gegenwart einer alkalisch puffernden Substanz ( $\text{Na}_2\text{HPO}_4$ , gemäß Stand der Technik) und einmal ohne alkalisch puffernde Substanz (erfindungsgemäß)
- Zwischenschicht, entweder erfindungsgemäß aus einem mit Alkalien auf pH 6,0 bzw. 7,0 teilneutralisierten enterischen Schichtmaterial, oder inertes Schichtmaterial, das gemäß Stand der Technik als puffernde Substanz Natriumacetat enthält. Das Referenzbeispiel enthält nicht neutralisiertes enterisches Schichtmaterial und Natriumacetat als puffernde Substanz.
- Außenschicht aus Eudragit® L100-55

Außerdem wurde bei einer Versuchsreihe eine Arzneiform getestet, in welcher die Zwischenschicht weggelassen wurde.

Die jeweiligen Pelletchargen wurden bei 40°C und 75% relativer Feuchte (rF) offen in einer Petrischale eine Woche und 20 Tage gelagert. Anschließend wurden der Omeprazolgehalt bzw. das Auftreten von Degradationsprodukt mit HPLC bestimmt. Die in Tabelle 2 zusammengestellten Werte stellen das Mittel von 3 Probenaufbereitungen dar.

Tabelle 2

Charge	Rezeptur	Gehalt Omeprazol [Gew.-%]			Degradationsprodukt von Omeprazol [Flächen-%]	
	Lagerungsbedingungen	40°C / 75 % rel. Feuchte				
	Lagerungsdauer	nach Herst.	1 Woche	20 Tage	nach Herst.	1 Woche
gemäß der Erfindung						
2 a	Omeprazol-Kern + Hilfsstoffe *, ZS.: 3% E. L 100-55 pH 7,0 msr: 30% E. L 100-55	100 ⇄	92 ⇄	84	< 0,4.	⇄ n.b.
2 b	Omeprazol-Kern + Hilfsstoffe *, ZS.: 3% E. L 100-55 pH 6,0 msr: 30% E. L 100-55	100 ⇄	93 ⇄	80	< 0,4	⇄ 2
Stand der Technik						
2 c	Omeprazol-Kern + Hilfsstoffe *, ZS.: 3% HPMC + NaOAc msr: 30% E. L 100-55	100 ⇄	89 ⇄	66	< 0,4	⇄ 5
2 d	Omeprazol-Kern + Hilfsstoffe *, ZS.: 3% HPMC msr: 30% E. L 100-55	100 ⇄	83 ⇄	57	< 0,4	⇄ 10
2 e	Omeprazol-Kern + Hilfsstoffe *, keine ZS. msr: 30% E. L 100-55	100 ⇄	84 ⇄	54	< 0,4	⇄ 10
Referenzbeispiel						
2 f	Omeprazol-Kern + Hilfsstoffe* +Na <sub>2</sub> HPO <sub>4</sub> ZS.: 3% HPMCP + NaOAc msr: 30% HPMCP	100 ⇄	73 ⇄	41	< 0,4	⇄ 16

\*Hilfsstoffe:

ZS:

E:

msr:

Mannit, HPC, Natriumlaurylsulfat

Zwischenschicht

Eudragit [Gew.-%, bezogen auf den Kern]

magensaftresistent(e Schicht) [Gew.-%, bezogen auf den Kern]

n.b.= nicht bestimmt

Im Vergleich zum Stand der Technik erhält man erfindungsgemäß eine deutlich stabilere Darreichungsform. Die erfindungsgemäßen Pellets weisen unter den beschriebenen verschärften Lagerbedingungen nach 1 Woche noch 93 Gew.-%, nach 20 Tagen 80 Gew.-% des Wirkstoffes Omeprazol in intakter Form auf. Selbst nach 4-wöchiger Lagerung wurde erfindungsgemäß noch ein Omeprazol-Gehalt von 67 Gew.-% festgestellt (nicht in Tabelle dargestellt. Demgegenüber beträgt der Omeprazol-Gehalt bei nicht erfindungsgemäßen Arzneiformen, das heißt solchen

- mit einer Zwischenschicht aus HPMC und NaOAc
  - mit einer Zwischenschicht aus HPMC
  - ohne eine Zwischenschicht
  - mit einer Zwischenschicht aus HPMCP und NaOAc
- nach 20 Tagen lediglich 66, 57, 54 und 41 Gew.-%.

### Beispiel 3

"Self-Repair-Mechanismus" der reaktiven Zwischenschicht

Verglichen wurden Pellets mit folgendem Aufbau:

- ohne Zwischenschicht (sogenannte Pelletkerne)
  - mit der erfindungsgemäßen reaktiven Zwischenschicht
  - mit einer inerten Zwischenschicht aus HPMC
- (Referenzbeispiel)

Zur besseren Beurteilung des Self-Repair-Mechanismus wurden die Pellets nicht mit dem äußeren enterischen Überzug versehen. Alle Pellettypen wurden in künstlichem Magensaft (pH 1,2) in einem Freisetzungsmodell der Europäischen Pharmakopoe (Basket) getestet. Die Zwischenschicht wurde auf pH 7,0, der oberen Grenze des bevorzugten Bereichs, teilneutralisiert.

Die Ergebnisse (ohne Pelletkerne ohne Zwischenschicht) sind in der folgenden Tabelle 3 zusammengefaßt:

Tabelle 3

Zeit (min)	Erfindungsgemäße Zwischenschicht (Eudragit® L100-55, pH 7,0 teilneutralisiert)								Referenzbeispiel (HPMC)	
	5 % Zwischenschicht 3 a		10 % Zwischenschicht 3 b		15 % Zwischenschicht 3 c		20 % Zwischenschicht 3 d		20 % Zwischenschicht 3 e	
	Pellets verfärbt (%)	Farbe des Mediums	Pellets verfärbt (%)	Farbe des Mediums	Pellets verfärbt (%)	Farbe des Mediums	Pellets verfärbt (%)	Farbe des Mediums	Pellets verfärbt (%)	Farbe des Mediums
1	10	leicht gelb	0	farblos	0	farblos	0	farblos	10	leicht gelb
5	50	grün-gelb	0	farblos	0	farblos	0	farblos	100	braun
10	80	bräunlich	5	fahl-gelb	0	farblos	0	farblos		
20	100	braun	30	gelblich	5	fahl-gelb	5	fahl-gelb		
30			50	grün-gelb	30	gelblich	5	fahl-gelb		
50			70	grün-braun	50	grün-gelb	10	leicht gelb		
70			80	bräunlich			10	leicht gelb		
90			100	braun						
100					70	grün-braun	10	leicht gelb		
120					80	bräunlich	30	gelblich		

Nach diesen Ergebnissen lösen sich Pellets ohne Zwischenschicht (als Vergleich) innerhalb von 2 Minuten vollständig auf. Das FreisetzungsmEDIUM weist eine stark braune Verfärbung auf.

Pellets mit der erfindungsgemäßen reaktiven Zwischenschicht bleiben dagegen in Abhängigkeit von der Schichtdicke (5 bis 20 Gew.-%, bezogen auf den Kern) der Zwischenschicht bis maximal 120 Minuten intakt. Das FreisetzungsmEDIUM weist nur eine geringfügige Verfärbung auf.

Pellets mit einer im Stand der Technik üblichen inerten Zwischenschicht (Referenzbeispiel) lösen sich auch bei maximaler Schichtdicke der Zwischenschicht innerhalb von 5 Minuten vollständig auf. Das FreisetzungsmEDIUM weist eine stark braune Verfärbung auf.

Diese Experimente belegen einen meßbaren Schutzmechanismus bei Pellets mit der erfindungsgemäßen Zwischenschicht im Gegensatz zu Pellets mit einer Zwischenschicht nach dem Stand der Technik. Dieser Schutzmechanismus bewirkt die reaktive Umwandlung der Zwischenschicht in eine magensaftresistente Schicht im magensaftsauren Medium. Dies wird umso schneller erfolgen, je näher der pH-Wert der teilneutralisierten Zwischenschicht bei 5,5 liegt.

Aus sämtlichen Untersuchungen in den Beispielen 1 bis 3 geht somit eindeutig hervor, daß gemäß der Erfindung eine Arzneiform mit einer überraschend verbesserten Stabilität im Vergleich zu der des Standes der Technik erhalten wird. Dieses Stabilitätsverhalten zeigt sich insbesondere bei erhöhter Temperatur und Feuchte (Verreibungsversuche), aber auch unter verschärften Lagerbedingungen von 40°C und 75% rF an Pellets.

Beispiel 4

## Freisetzungsverhalten verschiedener Pelletrezepturen

Wesentlich für eine gute Bioverfügbarkeit des Wirkstoffes ist seine möglichst rasche Freisetzung im oberen Dünndarmbereich, dh. in einem schwach sauren/neutralen Milieu. Zur Überprüfung des Freisetzungsverhaltens wurden Pellets mit verschiedenen Rezepturen in ein wässriges Medium mit einem pH-Wert von 5,8 als *in vitro* Modell für den oberen Dünndarm (künstlicher Darmsaft) eingebracht und das unter Rühren in die Umgebung freigesetzte Omeprazol mit HPLC in Abhängigkeit von der Zeit bestimmt (analog Pharmakopoe).

Die untersuchten Pelletrezepturen und die Freisetzungsergebnisse sind in der Tabelle 4 wiedergegeben:

**Tabelle 4**

Charge	Pelletrezeptur	Freigesetztes Omeprazol [%]		
	Freisetzungsdauer	30 min	45 min	60 min
<b>gemäß der Erfindung</b>				
4 a	Omeprazol-Kern + Hilfsstoffe*, ZS.: 3 % E. L 100-55 pH 7,0 msr: 30% E. L 100-55	72	84	89
4 b	Omeprazol-Kern + Hilfsstoffe*, ZS.: 3 % E. L 100-55 pH 6,0 msr: 30% E. L 100-55	40	81	88
<b>Vergleichsbeispiel</b>				
4 c	Omeprazol-Kern + Hilfsstoffe*, keine ZS. msr: 30% E. L 100-55	3	5	8
4 d	Omeprazol-Kern + Hilfsstoffe*, keine ZS. msr: 20% E. L 100-55	13	37	59

\*Hilfsstoffe: Mannit, HPC, Natriumlaurylsulfat  
 ZS: Zwischenschicht  
 E: Eudragit [Gew.-%, bezogen auf den Kern]  
 msr: magensaftresistent(e Schicht) [Gew.-%, bezogen auf den Kern]

Abbildung 3 zeigt eine graphische Darstellung der Ergebnisse.



Die Dicke der äußeren enterischen Schicht bei Pelletchargen 4 a, b und c ist jeweils gleich (30 Gew.-% bezogen auf den Pelletkern, entspricht ca 40  $\mu\text{m}$ ). Trotzdem zeigen überraschend die mit der erfindungsgemäßen, reaktiven Zwischenschicht versehenen Chargen 4 a und 4 b eine deutliche raschere Auflösung im künstlichen Darmsaft, als wenn keine Zwischenschicht vorhanden ist (Charge 4 c). Dies ist auch dann noch der Fall, wenn die enterische Überzugsschicht noch dünner ausgebildet ist (Charge 4 d, 20 Gew.-% bezogen auf den Pelletkern, entspricht ca 30  $\mu\text{m}$ ). Dies erlaubt bei den erfindungsgemäßen Arzneiformen die Dicke der äußeren enterischen Schicht weiter zu erhöhen, was eine verbesserte Arzneimittelsicherheit gegenüber bekannten Präparaten bietet, ohne daß das Freisetungsverhalten - wie an sich zu erwarten wäre - negativ beeinflußt wird.

#### Beispiel 5

##### Verbesserte Stabilität des wirkstoffhaltigen Kerns

Es wurden in der Reibschale Granulate aus Omeprazol mit verschiedenen Hilfsstoffen hergestellt. Nach offener Lagerung über 32 Tage bei 40°C und 75% relativer Feuchte wurde mit HPLC der Restgehalt Omeprazol sowie das Auftreten von Degradationsprodukt bestimmt. Als Hilfsstoffe wurden im alkalischen Milieu pufferndes  $\text{Na}_2\text{HPO}_4$ , Texapon, Lactose, L-HPC, mikrokristalline Cellulose und Mannit (Charge 5 b), sowie eine Kombination dieser Hilfsstoffe ohne  $\text{Na}_2\text{HPO}_4$  (Charge 5 c) eingesetzt. Diese Chargen wurden mit einem Omeprazolgranulat verglichen, das neben dem Wirkstoff als Hilfsstoffe nur HPC und Mannit (Charge 5 a) enthielt. Die Ergebnisse sind in Tabelle 5 wiedergegeben.

Tabelle 5

Charge	Rezeptur (Granulat)	Gehalt Omeprazol [Gew.-%]		Degradationsprodukt von Omeprazol [Flächen-%]	
	Lagerungsbedingungen	40°C / 75 % rel. Feuchte			
	Lagerungsdauer	nach Herst.	32 Tage	nach Herst.	32 Tage
erfindungsgemäß bevorzugt					
5 a	Omeprazol Mannit HPC	100	⇒	100	< 0,1    ⇒    < 0,5
Referenzbeispiel					
5 b	Omeprazol Hilfsstoffe Na <sub>2</sub> HPO <sub>4</sub>	100	⇒	100	< 0,1    ⇒    < 0,5
5 c	Omeprazol Hilfsstoffe ohne Na <sub>2</sub> HPO <sub>4</sub>	100	⇒	72	< 0,1    ⇒    ca.30

Erwartungsgemäß zeigt das Omeprazolgranulat ohne alkalisch reagierendem Zusatz (Charge 5 c) eine deutlich verschlechterte Lagerungsstabilität gegenüber einem Omeprazolgranulat mit Na<sub>2</sub>HPO<sub>4</sub> als Zusatz (Charge 5 b). So nimmt der Omeprazolgehalt auf 72 Gew.% ab, es entsteht ca. 30 Flächen-% Degradationsprodukt. Überraschenderweise zeigt ein Omeprazolgranulat mit Mannit und Hydroxypropylcellulose als einzige Hilfsstoffe, insbesondere ohne alkalisch reagierende Zusätze (Charge 5 a) ebenfalls eine hervorragende Lagerungsstabilität. In der erfindungsgemäß bevorzugten Arzneiform ist es daher nicht notwendig und auch nicht bevorzugt, alkalische reagierende Hilfsstoffe oder Omeprazolsalz im Kern zu verwenden, da gegebenenfalls aus dem Kern in die reaktive Zwischenschicht eindiffundierende alkalische Substanzen den "Self-Repair-Mechanismus", wie vorstehend erläutert, behindern können.

Beispiel 6

Herstellung von erfindungsgemäßen Arzneiformen

Rezepturbeispiele

Arzneiform A

Kern:

Omeprazol	210,00 g
Mannit	781,60 g
Hydroxypropylcellulose	3,30 g
Natriumlaurylsulfat	5,00 g

Zwischenschicht:

Eudragit® L100-55 mit	
NaOH auf pH 7,0 neutralisiert	50,00 g
Triethylcitrat	5,00 g

Magensaftresistente (Außen) Schicht:

Eudragit® L100-55	300,00 g
Triethylcitrat	30,00 g
Talkum mikronisiert	150,00 g

Arzneiform B

Kern:

Omeprazol	210,00 g
Mannit	781,60 g
Hydroxypropylcellulose	3,30 g
Natriumlaurylsulfat	5,00 g

Zwischenschicht:

Eudragit® L 100-55 mit	
NaOH auf pH 5,5 neutralisiert	50,00 g
Triethylcitrat	5,00 g
Talkum	15,00 g

Magensaftresistente (Außen) Schicht:

Eudragit® L100-55	400,00 g
Triethylcitrat	40,00 g
Talkum mikronisiert	200,00 g

Die vorgewogenen Komponenten Omeprazol, Mannit und Natriumlaurylsulfat werden in einem Mischer gegeben und vermischt. Eine Granulierungsflüssigkeit aus in Isopropanol gelöster Hydroxypropylcellulose wird langsam zu den vorgemischten Komponenten im Mischer unter konstantem Rühren zugegeben. Falls erforderlich, kann für eine bessere Pelletausbildung weiteres Isopropanol zugegeben werden. Die Mischzeit beträgt 10 bis 20 min, bis die Mehrzahl der Pellets eine erwünschte mittlere Größe von ca. 1000 µm haben.

Die feuchten Pellets werden in einem Trockner bei ca. 60°C für ca. 40 Min. getrocknet. Pellets mit einem Durchmesser von < 700 µm oder > 1200 µm werden ausgesiebt.

Die Pellets werden in einem fluidisierten Zustand gehalten, während zunächst eine Überzugsdispersion I und anschließend eine Überzugsdispersion II auf die Pellets mit einer konstanten Rate aufgesprüht wird.

Zur Herstellung der Überzugsdispersion I wird gereinigtes Wasser in ein Edelstahlgefäß gefüllt und Natriumhydroxid im Wasser aufgelöst. Die Natriumhydroxidlösung wird unter Rühren zum mikronisierten Talkum gegeben, dann wird eine Eudragitdispersion langsam zu der Natriumhydroxid/Talkumdispersion unter Rühren zugegeben, wobei Klumpen und Schaumbildung vermieden werden müssen. Nach Zugabe von Triethylcitrat zur Dispersion wird das Rühren für mindestens 15 min fortgesetzt, wobei hierbei der pH-Wert auf pH 7,0 bzw. pH 5,5 mit Natriumhydroxidlösung eingestellt wird. Während der Ausbildung des Überzugs muß die Dispersion kontinuierlich weitergerührt werden.

Zur Herstellung der Überzugsdispersion II wird mikronisiertes Talkum in gereinigtem Wasser dispergiert. Anschließend wird die so erhaltene wässrige Dispersion zur Eudragitdispersion unter Rühren zugesetzt, wobei Auftreten von Klumpen oder Schaum vermieden werden muß. Nach Zugabe von Triethylcitrat wird die Dispersion für mindestens weitere 15 min gerührt. Die

Omeprazolpellets werden dann in eine Beschichtungsapparatur überführt und bei 30°C zunächst mit der Überzugsdispersion I und dann mit der Überzugsdispersion II befilmt. Die fertigen Omeprazolpellets werden in Hartgelatine kapseln gefüllt.

### Beispiel 7

*In vitro* Versuche zur chemischen Stabilität der erfindungsgemäßen Arzneiform:

Es ist bekannt, daß Omeprazol bei längerer Lagerung an Wirksamkeit verliert, was auf einen Abbau der Wirksubstanz zurückzuführen ist. Durch Aufbringen geeigneter Schutzschichten kann dieser chemische Abbau von Omeprazol auf ein Minimum reduziert werden.

In Stabilitätsversuchen unter Streßbedingungen (40°C / 75 % rel. Feuchte) konnte gezeigt werden, daß die erfindungsgemäße Arzneiform bei Lagerung in verschlossenen braunen Schraubdeckelgläsern für 4 Wochen weniger als 2 Gew.-% Wirkstoff verliert (Mittelwerte von je drei Gehaltsbestimmungen). Ein unter identischen Bedingungen gelagertes Handelsprodukt verlor dagegen im gleichen Zeitraum mehr als 80 Gew.-% Wirkstoff (siehe Tabelle 6).

**Tabelle 6**

Arzneiform (Charge)	Omeprazolgehalt
	nach 12 Wochen Lagerung bei 40°C/75% r.F. im verschlossenen Schraubdeckelglas [Gew.-%]
<b>gemäß der Erfindung</b>	
6 a	98,9
6 b	98,3
6 c	99,3
<b>Handelsprodukt</b>	
6 d	16,2

In weiteren Stabilitätsversuchen unter Langzeit- und Streßbedingungen (25°C / 60 % r.F.; 30°C / 60 % r.F.; 40°C / 75 % r.F.) konnte gezeigt werden, daß die erfindungsgemäße Arzneiform bei Lagerung im Primärpackmittel für 12 Wochen weniger als 5 Gew.-% Wirkstoff verliert (Mittelwerte von je drei Gehaltsbestimmungen). Die Ergebnisse sind in Tabelle 7 dargestellt.

**Tabelle 7**

Arzneiform (Charge)	Omeprazolgehalt		
	nach 12 Wochen Lagerung [Gew.-%]		
Lagerungsbedingungen	25°C/60% r.F.	30°C/60% r.F.	40°C/75% r.F.
7 a	98,9	97,9	97,8
7 b	99,1	97,8	95,3
7 c	100,5	103,3	98,0

Die Ergebnisse zeigen deutlich, daß bei der erfindungsgemäßen Arzneiform keine signifikante Gehaltsabnahme vom Ausgangswert festzustellen war.

Beispiel 8

## Bestimmung der Magensaftresistenz

Zur Bestimmung der Magensaftresistenz wurden Proben der erfindungsgemäßen Arzneiform gemäß Beispiel 6 einem *in vitro* Test unterzogen. Dabei wurde die jeweilige Probe, die sich in einem Basket befand, bei pH 1,2 und einer Temperatur von 37°C sowie 100 upm des Basket in dem sauren Medium für 120 min belassen und anschließend die Probe auf den verbleibenden Wirkstoffgehalt analysiert. Die dabei erhaltenen Werte sind in Tabelle 8 zusammengefaßt. Sämtliche Werte zeigen, daß sich unter den gewählten Bedingungen kein signifikanter Abbau zum Ausgangswert ergibt.

Tabelle 8

Arzneiform (Charge)	Omeprazolrestgehalt [Gew.-%]
gemäß der Erfindung	
8 a	98,4
8 b	98,9
8 c	96,0

Beispiel 9*In vitro* Untersuchungen zur Wirkstoff-Freisetzung

Für die folgenden Versuche wurde ebenfalls eine erfindungsgemäße Arzneiform gemäß Beispiel 6 untersucht. Die jeweilige Probe, die sich in einem Basket befand, wurde 120 Minuten lang bei 37°C einem Medium (1000 ml) von pH 1,2 ausgesetzt.

Nach der vorstehend genannten Verweilzeit in saurem Medium wurde dieses durch ein alkalisches Medium (pH 6,8, phosphatgepuffert) ersetzt, und die Probe jeweils für einen Zeitraum von 5, 10, 15, 20, 30, 60 Minuten darin belassen. Nach den genannten Zeitintervallen wurden Analysen zum freigesetzten Wirkstoff durchgeführt.

Die Bestimmung der *in vitro* Wirkstoff-Freisetzung erfolgte an Proben vor ihrer Einlagerung (Abbildung 4) und nach einer zwölfwöchigen Lagerung bei 25°C/60% r.F. (Abbildung 5), bei 30°C/60% r.F. (Abbildung 6) und 40°C/75% r.F. (Abbildung 7). Die Arzneimittel wurden zuvor in das vorgesehene Packmittel abgefüllt. Die erhaltenen Werte sind für die jeweiligen erfindungsgemäßen Chargen in den Abbildungen 4 bis 7 dargestellt, und zeigen, daß über den Lagerzeitraum die Freisetzung stabil ist.

Beispiel 10

Kombinationspräparat Omeprazol und Diclofenac

Kapselformulierung C:

Eine Kapsel enthält 210 mg Diclofenac-Pellets entsprechend 75 mg Diclofenac-Na und 160 mg Omeprazol-Pellets entsprechend 20 mg Omeprazol. Sowohl die Diclofenac-Pellets als auch die Omeprazol-Pellets wurden nach dem Herstellungsverfahren gemäß Beispiel 6 hergestellt.

Kapselformulierung D:

Eine Kapsel enthält 420 mg Diclofenac-Pellets entsprechend 150 mg Diclofenac-Na und 160 mg Omeprazol-Pellets entsprechend 20 mg Omeprazol, die gemäß Beispiel 6 hergestellt wurden. Die Diclofenac-Pellets wurden nach dem in EP 0 348 808 wiedergegebenen Verfahren hergestellt.



**Patentansprüche**

1. Stabile Arzneiform zur oralen Verabreichung, welche
  - (a) einen Kern, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit üblichen pharmazeutischen Hilfsstoffen enthält,
  - (b) eine auf den Kern aufgebrachte Zwischenschicht, und
  - (c) eine magensaftresistente Außenschicht umfaßt,  
**dadurch gekennzeichnet, daß**  
in (b) eine reaktive Zwischenschicht aus einem mit Alkalien teilneutralisierten magensaftresistenten Polymer-Schichtmaterial mit Kationenaustauscher-kapazität vorliegt.
2. Arzneiform nach Anspruch 1, dadurch gekennzeichnet, daß die Alkalien ausgewählt sind aus Natriumhydroxid und Kaliumhydroxid.
3. Arzneiform nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß der pharmazeutische Hilfsstoff ausgewählt ist aus Mannit und Hydroxypropylcellulose.
4. Arzneiform nach Anspruch 1 bis 3, dadurch gekennzeichnet, daß der Kern zusätzlich ein Netzmittel umfaßt.
5. Arzneiform nach Anspruch 4, dadurch gekennzeichnet, daß das Netzmittel ausgewählt ist aus Natriumlaurylsulfat, Sorbitanfettsäureester und Polyoxyethylensorbitan-Fettsäureester.
6. Arzneiform nach Anspruch 1 bis 5, dadurch gekennzeichnet, daß der Kern in Form von Pelletkernen, Tabletten, Mikrotabletten oder als Granulat vorliegt.
7. Arzneiform nach Anspruch 1 bis 6, dadurch gekennzeichnet, daß das magensaftresistente Polymer-Schichtmaterial in der reaktiven Zwischenschicht auf einen pH-Bereich von ca.

5,5 bis ca. 7,0, bevorzugt 5,5 bis 6,5, teilneutralisiert ist.

8. Arzneiform nach Anspruch 7, dadurch gekennzeichnet, daß das teilneutralisierte magensaft-resistente Polymer-Schichtmaterial ausgewählt ist aus teilneutralisiertem Eudragit® L100-55, Eudragit® L100, Hydroxypropylmethylcellulosephthalat (HPMCP) und Celluloseacetatphthalat (CAP).
9. Arzneiform nach Anspruch 1 bis 8, dadurch gekennzeichnet, daß die reaktive Zwischenschicht zusätzlich einen Weichmacher umfaßt.
10. Arzneiform nach Anspruch 9, dadurch gekennzeichnet, daß der Weichmacher ausgewählt ist aus Triethylcitrat, Acetyltriethylcitrat, acetylierten Monoglyceriden, Propylenglykol und Polyethylenglykolen.
11. Arzneiform nach Anspruch 1 bis 10, dadurch gekennzeichnet, daß die reaktive Zwischenschicht beim Eindringen von Protonen durch die Außenschicht eine gelartige Schicht ausbildet.
12. Arzneiform nach Anspruch 1 bis 11, dadurch gekennzeichnet, daß die reaktive Zwischenschicht eine Dicke von 5 bis 30µm besitzt.
13. Arzneiform nach Anspruch 1 bis 12, dadurch gekennzeichnet, daß die magensaftresistente Außenschicht in (c) Eudragit® L100-55, Eudragit® L100, Hydroxypropylmethylcellulosephthalat (HPMCP) und/oder Celluloseacetatphthalat (CAP) enthält.
14. Arzneiform gemäß Anspruch 13, dadurch gekennzeichnet, daß die magensaftresistente Außenschicht pharmazeutisch verträgliche Antihaftmittel, Dispergierungsmittel, Pigmente und/oder Farbstoffe enthält.

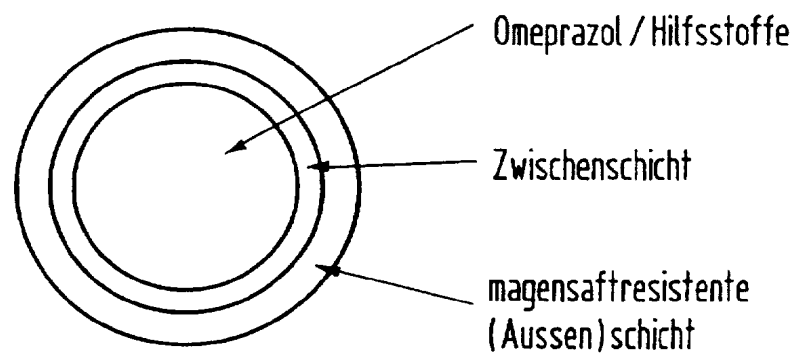
15. Arzneiform nach Anspruch 14, dadurch gekennzeichnet, daß das Antihaftmittel Talkum ist.
16. Arzneiform nach Anspruch 1 bis 15, dadurch gekennzeichnet, daß die magensaftresistente Außenschicht eine Schichtdicke von 20 bis 60  $\mu\text{m}$ , bevorzugt 30 bis 60  $\mu\text{m}$  aufweist.
17. Arzneiform nach Anspruch 1 bis 16, welche
  - (a) einen Kern, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit Mannit und Hydroxypropylcellulose als Hilfsstoffe ohne alkalische Zusätze enthält,
  - (b) eine auf den Kern aufgebrachte reaktive Zwischenschicht mit einer Dicke von 5 bis 30  $\mu\text{m}$  aus mit Natriumhydroxid auf einen pH-Bereich von ca. 5,5 bis ca. 7,0 teilneutralisiertem Eudragit® L100-55, und
  - (c) eine magensaftresistente Außenschicht mit einer Dicke von 30 bis 60  $\mu\text{m}$  aus Eudragit® L100-55 umfaßt.
18. Arzneiform nach Anspruch 1 bis 17, dadurch gekennzeichnet, daß die reaktive Zwischenschicht als eine Vielzahl von Einzelschichten ausgebildet ist.
19. Arzneiform nach Anspruch 1 bis 18, dadurch gekennzeichnet, daß die magensaftresistente Außenschicht als eine Vielzahl von Einzelschichten ausgebildet ist.
20. Arzneiform nach Anspruch 1 bis 19, dadurch gekennzeichnet, daß der pH-Übergang an der Grenze von der magensaftresistenten Außenschicht zur reaktiven Zwischenschicht als Gradient ausgebildet ist.
21. Verfahren zur Herstellung einer stabilen Arzneiform zur oralen Verabreichung nach einem der Ansprüche 1 bis 20, dadurch gekennzeichnet, daß man

- (a) als Kern einen Formling bildet, der einen Wirkstoff, ausgewählt aus Omeprazol, Lansoprazol und Pantoprazol, zusammen mit üblichen pharmazeutischen Hilfsstoffen enthält
  - (b) auf die Formlinge eine Zwischenschicht aufbringt, und
  - (c) die so überzogenen Formlinge mit einer magensaftresistenten Schicht befilmt, dadurch gekennzeichnet, daß man in (b) eine reaktive Zwischenschicht aus einem mit Alkalien teilneutralisierten magensaftresistenten Polymer-Schichtmaterial mit Kationenaustauscher-kapazität aufbringt.
22. Verfahren nach Anspruch 21, dadurch gekennzeichnet, daß man das magensaftresistente Polymer-Schichtmaterial vor dem Aufsprühen auf den Kern mit Alkalien auf einen pH-Bereich von ca. 5,5 bis ca. 7,0 teilneutralisiert.
23. Verfahren nach Anspruch 22, dadurch gekennzeichnet, daß man als Alkalien Natriumhydroxid oder Kaliumhydroxid verwendet.
24. Verfahren nach Anspruch 21, dadurch gekennzeichnet, daß man in Schritt (a) Isopropanol als ein Lösungsmittel verwendet.
25. Pharmazeutische Zusammensetzung, welche zusätzlich zu einer stabilen Arzneiform nach Anspruch 1 bis 20 Diclofenac als weiteren Wirkstoff enthält.
26. Pharmazeutische Zusammensetzung nach Anspruch 25, dadurch gekennzeichnet, daß das Diclofenac als Formulierung vorliegt, welche
- (a) einen Diclofenac-haltigen Kern zusammen üblichen Hilfsstoffen,

- (b) eine auf den Kern aufgebrachte reaktive Zwischenschicht aus mit Alkalien teilneutralisiertem magensaftresistenten Polymer-Schichtmaterial, und
  - (c) eine magensaftresistente Außenschicht umfaßt.
27. Pharmazeutische Zusammensetzung nach Anspruch 25, dadurch gekennzeichnet, daß das Diclofenac als Pelletformulierung umfassend eine Mischung von magensaftresistent umhüllten Pellets und retardiert durchlässigen Pellets vorliegt.
28. Pharmazeutische Kapselformulierung, dadurch gekennzeichnet, daß sie eine stabile Arzneiform nach Anspruch 1 bis 20 oder eine Zusammensetzung nach Anspruch 25 bis 27 als Pellets enthält.

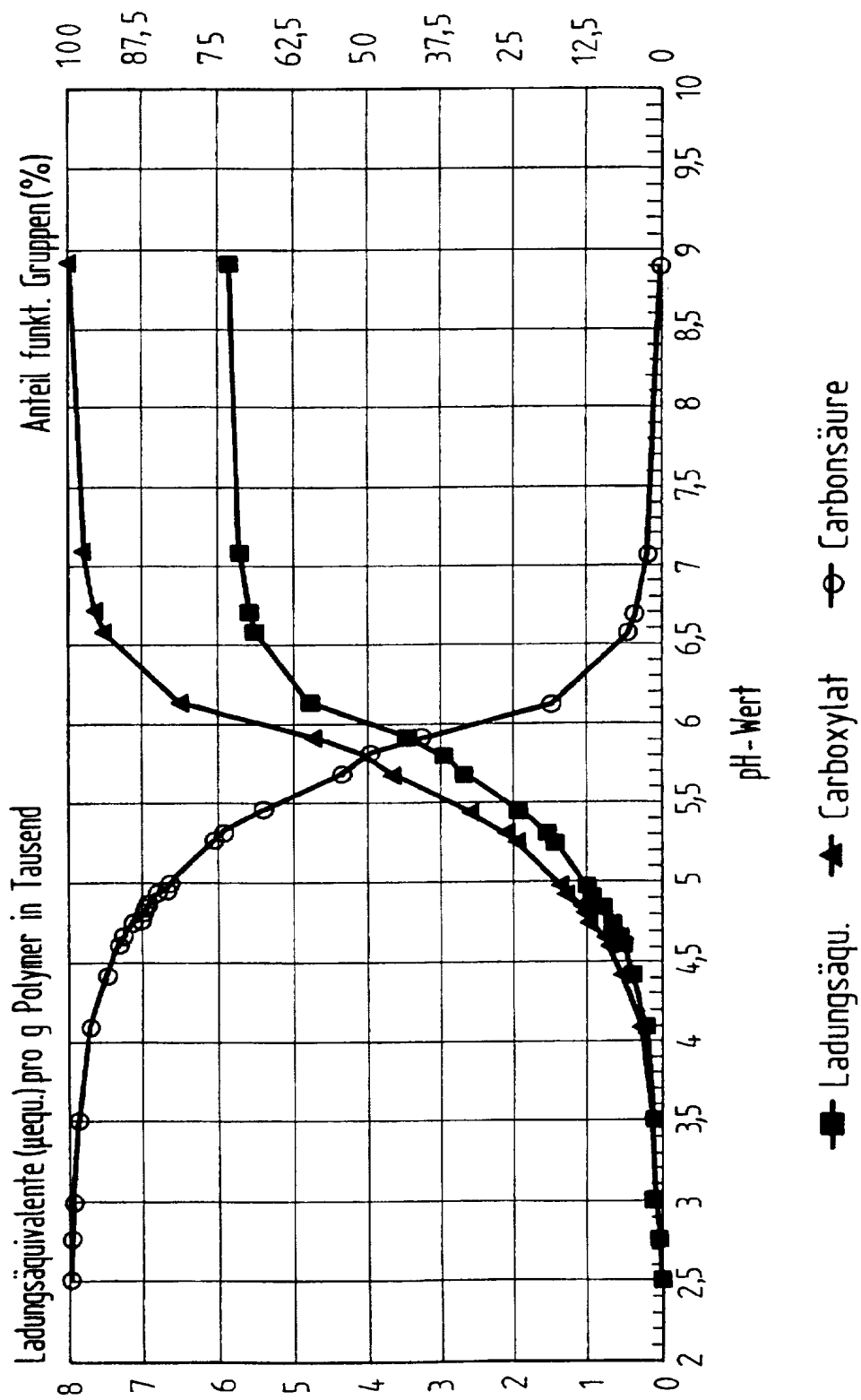
# Abb. 1

Schematischer Schichtaufbau gemäß der Erfindung



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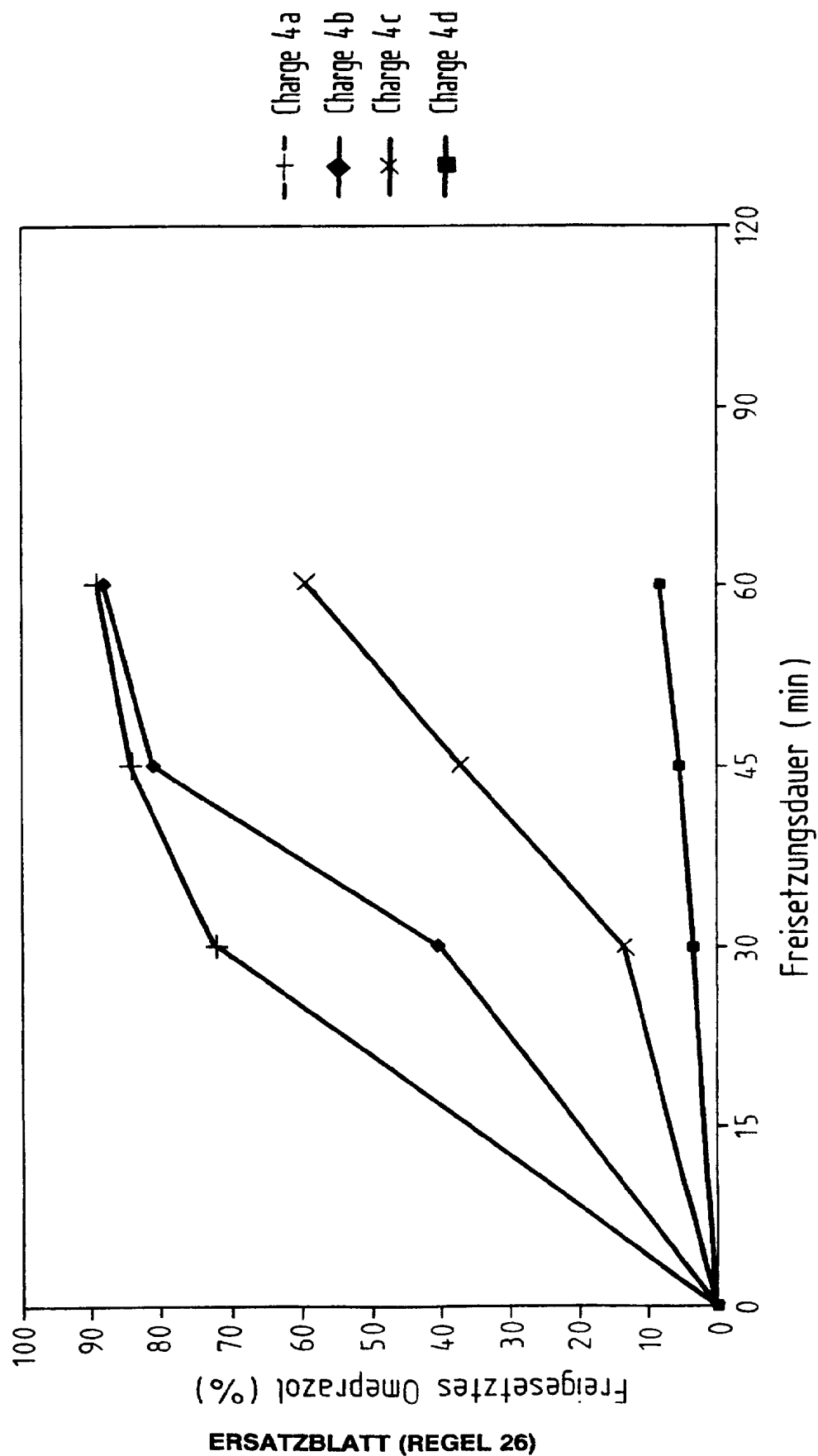
Abb. 2



3 / 7

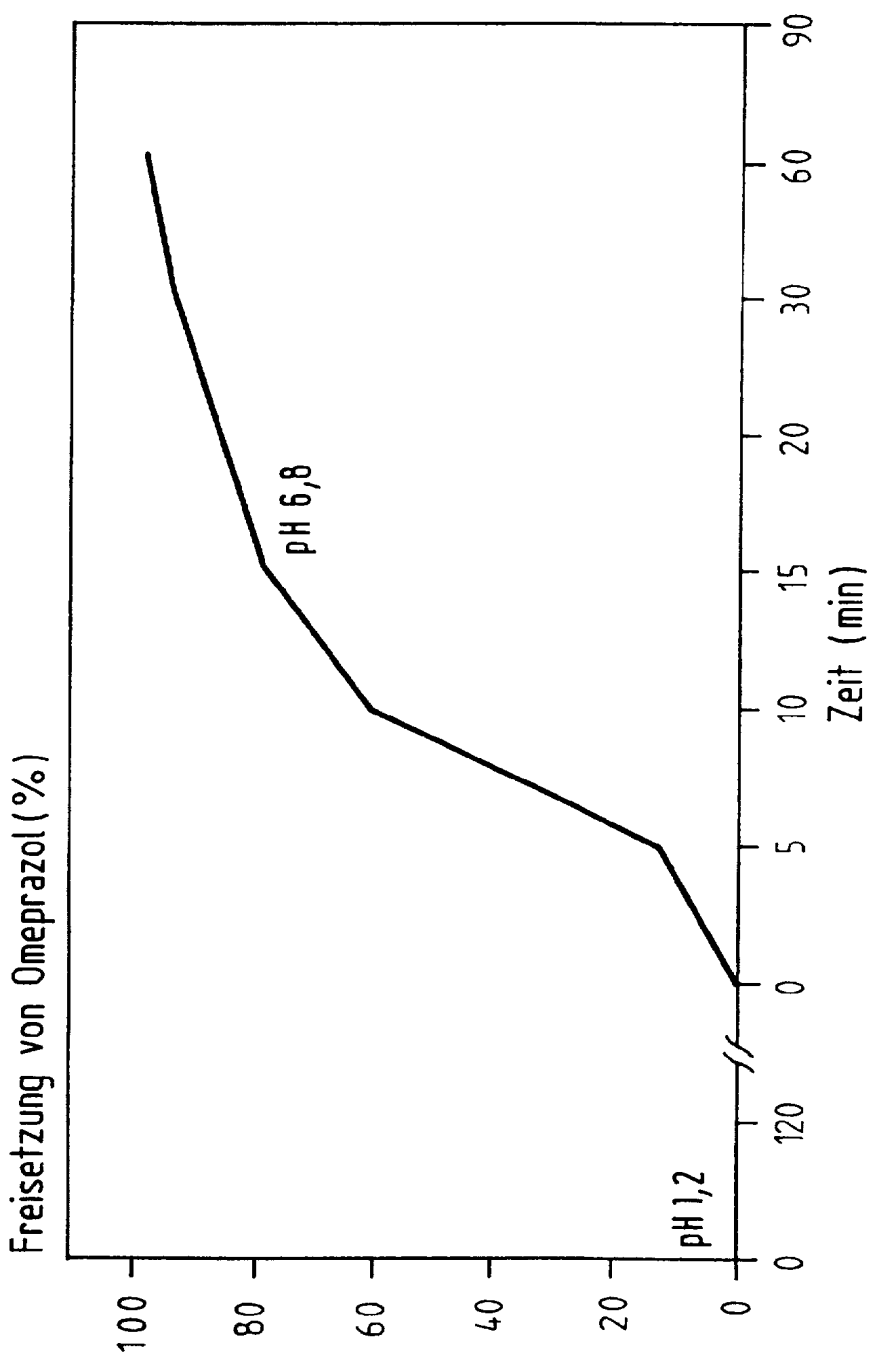
Abb. 3

Freisetzung verschiedener Pelletrezepturen bei pH 5,8

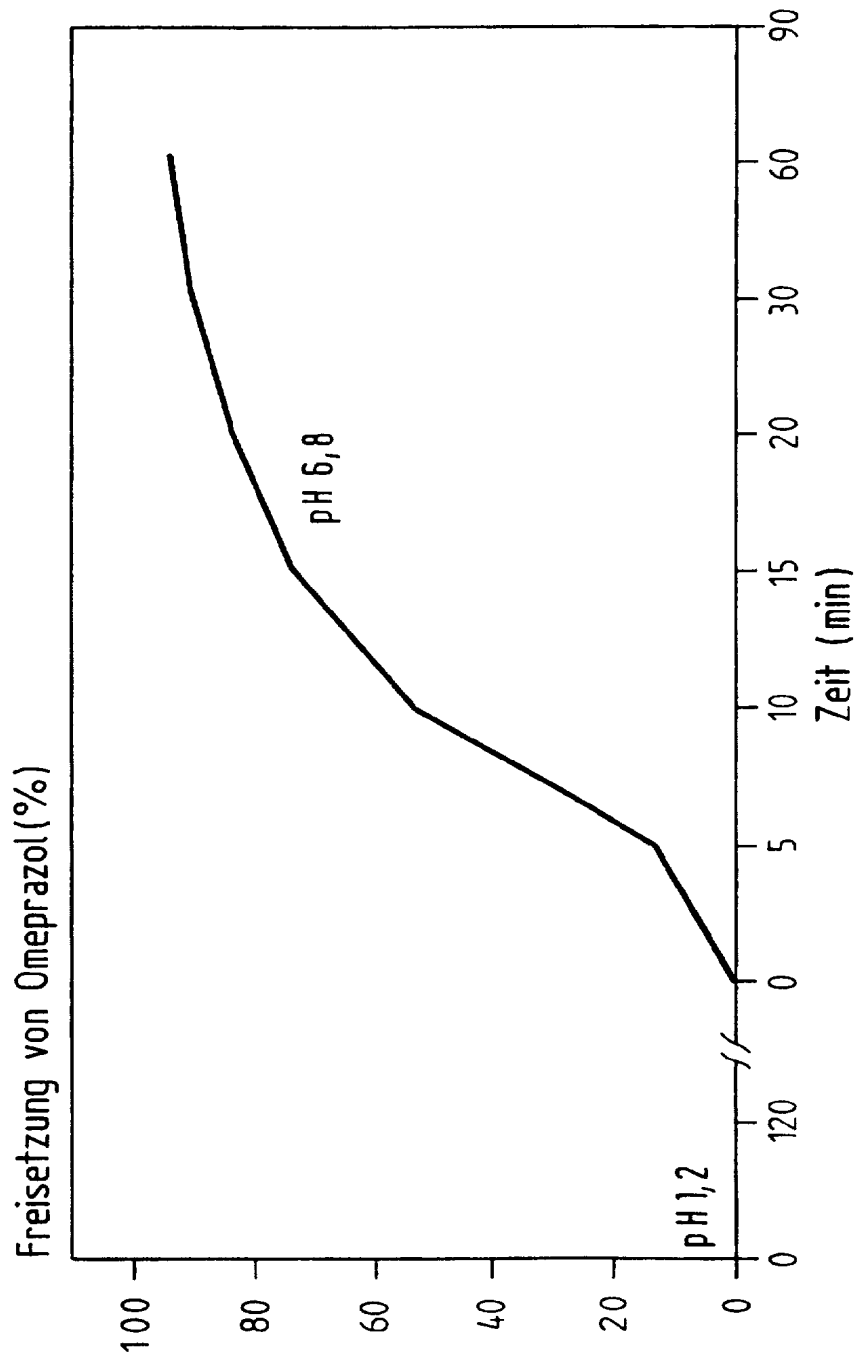




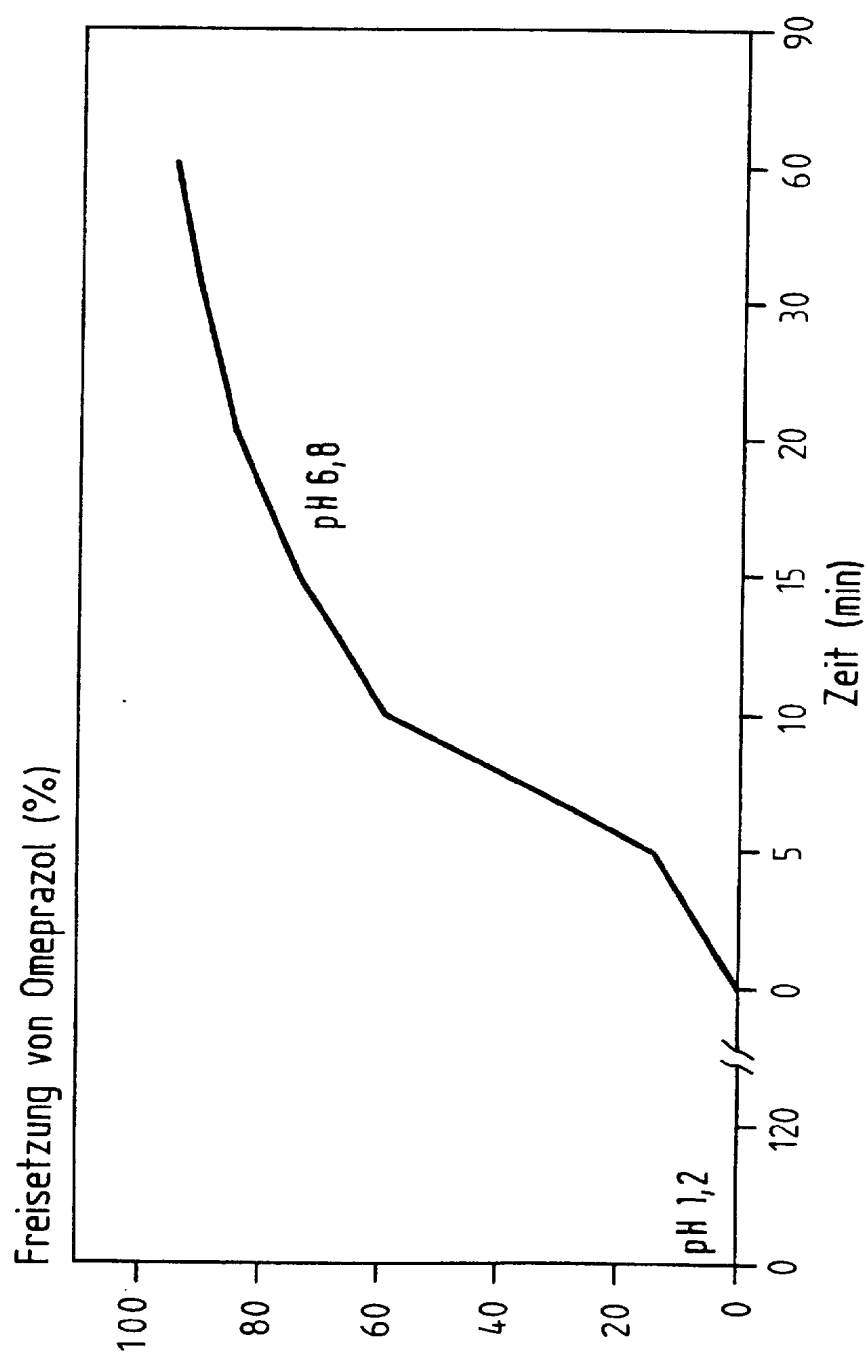
**Abb. 4** Freisetzung Omeprazol - Pellets  
120 Minuten pH 1,2 - 60 Minuten pH 6,8  
Ausgangswerte



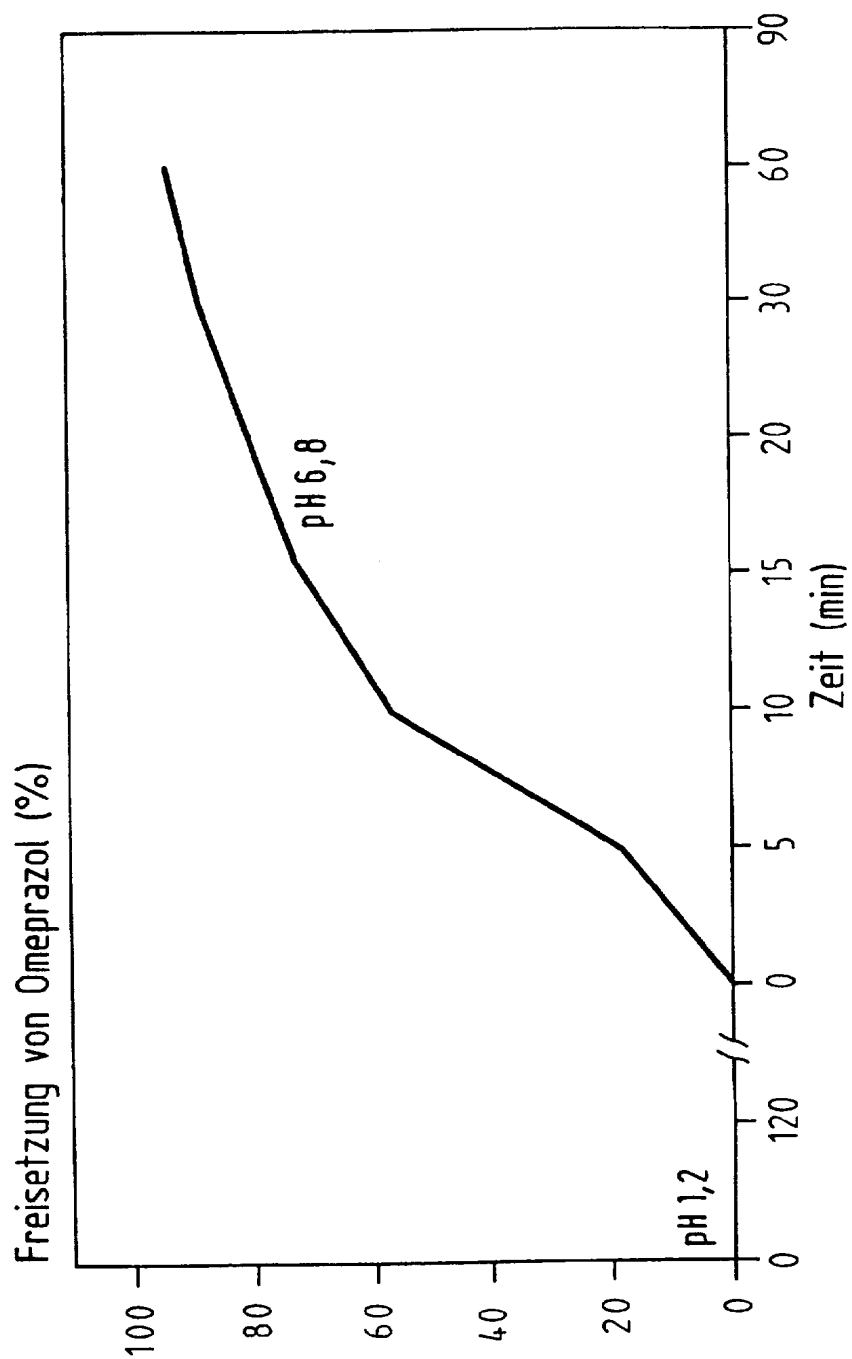
**Abb. 5** Freisetzung Omeprazol - Pellets  
120 Minuten pH 1,2 - 60 Minuten pH 6,8  
nach 12-wöchiger Lagerung bei 25°C/60% r.F.



**Abb. 6**  
**Freisetzung Omeprazol - Pellets**  
120 Minuten pH 1,2 - 60 Minuten pH 6,8  
nach 12-wöchiger Lagerung bei 30°C/60% r.F.



**Abb. 7** Freisetzung Omeprazol - Pellets  
120 Minuten pH 1,2 - 60 Minuten pH 6,8  
nach 12-wöchiger Lagerung bei 40°C/60% r.F.





**PCT**  
WELTORGANISATION FÜR GEISTIGES EIGENTUM  
Internationales Büro  
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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<b>(21) Internationales Aktenzeichen:</b> PCT/EP97/03534 <b>(22) Internationales Anmeldedatum:</b> 4. Juli 1997 (04.07.97) <b>(30) Prioritätsdaten:</b> 196 28 643.3      16. Juli 1996 (16.07.96)      DE <b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b> MERCK PATENT GMBH [DE/DE]; D-64271 Darmstadt (DE). <b>(72) Erfinder; und</b> <b>(75) Erfinder/Anmelder (nur für US):</b> HOSTALEK, Martin [DE/DE]; Auf der Haardt 54a, D-64291 Darmstadt (DE). BÜTTNER, Werner [DE/DE]; Im Erlich 6, D-64291 Darmstadt (DE). BRAUN, Jürgen [DE/DE]; Schlesierstrasse 38, D-64839 Altheim (DE). <b>(74) Gemeinsamer Vertreter:</b> MERCK PATENT GMBH; D-64271 Darmstadt (DE).		<b>(81) Bestimmungsstaaten:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>
<b>(54) Title: MATERIALS FOR PRODUCTION OF CONTAINERS</b> <b>(54) Bezeichnung: WERKSTOFFE FÜR DIE HERSTELLUNG VON TRANSPORTBEHÄLTERN</b> <b>(57) Abstract</b> <p>The invention relates to the use of polyethylene materials for the production of solid storage and transportation containers, and also for the production of lined storage and transportation containers for chemicals, and in particular for transportation and storage of high-purity, liquid chemicals for the electronics industry. The invention also relates to the use of said materials for producing equipment which is required to remove the chemicals from said containers.</p> <b>(57) Zusammenfassung</b> <p>Die Erfindung betrifft die Verwendung von Polyethylen-Werkstoffen für die Herstellung von massiven Lager- und Transportbehältern aber auch für die Herstellung von ausgekleideten Lager- und Transportbehältern für Chemikalien, und zwar insbesondere für den Transport und die Lagerung von hochreinen, flüssigen Chemikalien für die Elektronikindustrie. Weiterhin betrifft die Erfindung die Verwendung dieser Werkstoffe zur Herstellung des Equipments, welches zur Entnahme der Chemikalien aus den Transportbehältern notwendig ist.</p>		

### LEDIGLICH ZUR INFORMATION

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## **Werkstoffe für die Herstellung von Transportbehältern**

Die Erfindung betrifft die Verwendung von Polyethylen-Werkstoffen für die Herstellung von massiven Transport- und Lagerbehältern aber  
5 auch für die Herstellung von ausgekleideten Transport- und Lagerbehältern für Chemikalien, und zwar insbesondere für den Transport und die Lagerung von hochreinen, flüssigen Chemikalien für die Elektronikindustrie. Weiterhin betrifft die Erfindung die Verwendung dieser Werkstoffe zur Herstellung des Equipments,  
10 welches zur Entnahme der Chemikalien aus den Transportbehältern sowie zu deren Befüllung notwendig ist .

Bei der Herstellung von elektronischen Bauelementen werden in vielen Fällen flüssige Chemikalien benötigt, an deren Reinheit  
15 höchste Ansprüche gestellt werden. Dieses ist besonders für die Herstellung hochintegrierter Mikrochips der Fall. Einerseits liegt die Reinheit dieser Chemikalien in einem Bereich, bei dem es nicht mehr genügt, die Chemikalien in der geforderten Reinheit herzustellen, sondern es muß auch dafür gesorgt werden, daß beim Transport, während der Lagerung und der Handhabung keine Verunreinigungen  
20 mehr in das Produkt gelangen. Andererseits muß die Lager- und Transportsicherheit gewährleistet sein, da einige dieser Chemikalien aufgrund ihrer aggressiven Eigenschaften schwierig zu handhaben und zu lagern sind. Auch sind sie in vielen Fällen toxikologisch nicht unbedenklich oder aufgrund ihrer chemischen Eigenschaften  
25 schädlich. Ein unbeabsichtigtes Ausfließen, z. B. aufgrund einer Beschädigung des Transportbehälters oder aufgrund von Undichtigkeiten, hervorgerufen durch die aggressiven Eigenschaften einiger dieser Chemikalien, muß mit hoher Sicherheit ausgeschlossen werden.

30 Die Materialauswahl für derartige Transportbehälter muß sich aufgrund der Anforderungen an die zu transportierenden Chemikalien in erster Linie danach richten, jegliche Verunreinigungen auszuschließen. Diese Anforderung wird in der Regel von Behältern  
35 aus fluorierten oder perfluorierten Werkstoffen oder von Behältern, die mit solchen Werkstoffen ausgekleidet sind, erfüllt.

Je nach Anforderungen werden diese Transport- und Lagerbehälter als drucklose Version oder auch als Druckbehälter hergestellt.

Drucklose Behälter dürfen keinem von außen aufgetragenen Innendruck ausgesetzt werden.

Aus solchen Behältern muß die Entnahme der flüssigen Chemikalien ebenfalls drucklos erfolgen, d. h. mit Hilfe von Pumpen. Diese Pumpen weisen zwangsläufig bewegte Teile auf, so daß Verunreinigungen durch im Pumpenbereich entstehenden Abrieb nicht völlig ausgeschlossen werden können.

Es ist jedoch insbesondere bei der Verwendung von druckfesten Behältern bekannt, Chemikalien mit Hilfe von Tauchrohren durch Zuführung von inerten Druckgasen zu entnehmen, so daß keine Pumpen benötigt werden und somit kein Abrieb entstehen kann. Aus DE 36 36 886 ist ein Transportbehälter für flüssige, hochreine Chemikalien mit einem zweischaligen Innenbehälter bekannt, dessen innerste Auskleidung aus einem Fluorkunststoff besteht. Dieser Transportbehälter ist durch seinen mehrschaligen Aufbau so dimensioniert, daß er mit einem Druck beaufschlagt werden kann. Nachteilig ist jedoch, daß einerseits zur Herstellung solcher Innenauskleidungen nur spezielle Fluorkunststoffe geeignet sind, die in aufwendigen und daher teuren Verfahren hergestellt werden müssen, und daß andererseits die Verarbeitbarkeit dieser Kunststoffe erschwert ist, da aufgrund der hohen Reinheitsanforderungen an die zu transportierenden Chemikalien dem Kunststoff keine beliebigen Verarbeitungshilfsmittel zugesetzt werden können und eine Kontamination durch Werkzeuge und Umwelteinflüsse weitgehend minimiert werden muß..

Bei der Materialauswahl für die Herstellung massiver Transportbehälter muß der polymere Werkstoff neben der Beständigkeit gegen mögliches Auslaugen und Verspröden durch zu transportierende Chemikalien zusätzlich sowohl eine ausreichende Steifigkeit als auch eine gewisse Elastizität aufweisen, so daß aus dem Werkstoff hergestellte Behälter gegenüber Druck und Stoß



unempfindlich und stabil sind und weder zur Verformung noch zur Rißbildung neigen. Weiterhin müssen diese Materialeigenschaften auf Dauer erhalten bleiben, so daß auch bei längerer Lagerung sowohl die Reinheit der zu transportierenden Chemikalien als auch die Behältereigenschaften erhalten bleiben.

Aufgabe der Erfindung ist es daher, einen geeigneten Werkstoff zur Herstellung von Transportbehältern für flüssige, hochreine Chemikalien und des notwendigen Equipments zur Verfügung zu stellen, der preiswert herzustellen ist, während der Synthese in hoher Reinheit erhalten wird, keine oder nur in sehr geringer Konzentration Polymerisationskatalysatoren enthält, sich in einfacher Weise möglichst ohne Zusatz von Verarbeitungshilfsmitteln verarbeiten läßt, bzw. nur solche Verarbeitungshilfsmittel enthält, die sich im Gebrauch nicht störend auswirken, oder die durch die zu transportierenden Chemikalien nicht aus dem Werkstoff ausgelaugt werden. Aufgabe der Erfindung ist es auch, einen geeigneten polymeren Werkstoff zur Verfügung zu stellen, aus dem sowohl massive Lager- und Transportbehälter für flüssige, hochreine Chemikalien als auch Auskleidungen für entsprechende Behälter, die mit Druck beaufschlagt werden können, herstellbar sind.

Die Aufgabe wird erfindungsgemäß gelöst durch die Verwendung von HD-Polyethylen (HD = high density) zur Herstellung von massiven Lager- und Transportbehältern für flüssige, hochreine Chemikalien für die Elektronikindustrie, des dazugehörigen Equipments, sowie von Auskleidungen für entsprechende Behälter, die mit Druck beaufschlagt werden können, und des hierzu benötigten Equipments. Insbesondere wird die Aufgabe gelöst durch die Verwendung von HD-Polyethylen mit einer spezifischen Dichte von 0,940 - 0,970 g/cm<sup>3</sup>, insbesondere von 0,942 - 0,961 g/cm<sup>3</sup>.

Als Werkstoffe für Behälter in denen hochreine Säuren oder Basen transportiert werden sollen kommen nach gängiger Meinung nur Kunststoffe in Frage, die auf fluorierten Kohlenwasserstoffen basieren. Solche Werkstoffe sind beispielsweise Polytetrafluorethylen (PTFE), Perfluor-Alkoxy-Polymere (PFA), Polyvinylidenfluoride

(PVDF), oder Poly(ethylen-Chlor-trifluorethylen) (ECTFE) und werden im allgemeinen Sprachgebrauch mit dem bekannten Warenzeichen „Teflon“ umschrieben. Für den Fachmann sind unter diese Begriff fallende Kunststoffe gegenüber dem Einfluß von aggressiven

5 Chemikalien, wie besonders starke Säuren oder Basen aber auch gegenüber Temperatureinflüssen unempfindlich. Es handelt sich bei diesen Kunststoffen um teure, und daher nicht wirtschaftliche Materialien.

10 Versuche haben nun überraschenderweise gezeigt, daß auch nicht fluorierte Kunststoffe zur Herstellung qualitativ hochwertiger Transportbehälter und des dazu gehörenden Equipments, wie z. B. Tauchrohre, Teile von Pumpen und Schläuche, für flüssige, hochreine Chemikalien für die Elektronikindustrie verwendet werden können.

15 Als besonders geeignete Werkstoffe für die gewünschte Verwendung haben sich ausgewählte HD-Polyethylene (high density polyethylen) erwiesen, und zwar solche Polyethylene mit einer spezifischen Dichte im Bereich von 0,940 - 0,970 g/cm<sup>3</sup>, insbesondere von 0,942 - 0,961 g/cm<sup>3</sup>. Weiterhin zeichnen sich diese Polyethylenqualitäten in der

20 Analyse durch einen besonders niedrigen Gehalt an Katalysatorresten aus. Daher werden von diesen Werkstoffen im Vergleich zu anderen im Kontakt mit sowohl basischen als auch sauren, hochreinen Chemikalien besonders geringe Mengen ionischer Verunreinigungen abgegeben. Auch werden im Kontakt mit

25 Chemikalien vergleichsweise wenig Partikel durch Wechselwirkungen zwischen den Chemikalien und dem Werkstoff erzeugt. Dieses ist besonders wichtig im Hinblick auf die Verwendung des Werkstoffs für die Herstellung des Equipments zum Befüllen und zur Entnahme der Chemikalien. Diese Werkstoffe sind überraschenderweise sowohl zur

30 Herstellung von Tauchrohren als auch für die Herstellung von Pumpen geeignet, die für die Entnahme der hochreinen Chemikalien aus drucklosen Transportbehältern und zum Fördern an den Verarbeitungsplatz benötigt werden.

35 Dieses war besonders überraschend, da sich entsprechende andere Polyethylen-Werkstoffe, die bereits seit langen Jahren für den Gefahrguttransport bewährt haben, als nicht geeignet für den

Transport und die Lagerung von hochreinen, flüssigen Chemikalien eignen. Im Test wurde bei diesen Kunststoffen sowohl eine zu hohe Partikelabgabe als auch eine nicht akzeptable Abgabe von ionogenen Verunreinigungen ermittelt.

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Als besonders geeignete Werkstoffe für den genannten Zweck haben sich Polyethylen-Werkstoffe erwiesen, die von der Firma BASF unter dem Warenzeichen Lupolen im Handel vertrieben werden.

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Insbesondere haben sich in Lagertests aus dieser Gruppe von Polyethylenspezifikationen Werkstofftypen als geeignet erwiesen, die unter den Bezeichnungen Lupolen 6021 D, Lupolen 5021 D, Lupolen 4261 A Q149, und Lupolen 4261 A Q 135 im Handel erhältlich sind.

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Für die erfindungsgemäße Verwendung sind diese Werkstoffe besonders geeignet, weil sie extrudierbar sind, sich aber auch ohne Qualitätsverlust verschweißen lassen. Hierdurch ergibt sich die Möglichkeit, durch Verschweißen von geeigneten Platten aus diesem Werkstoff Behälter in nahezu beliebiger Größe herzustellen. Durch auf einer Seite dieser Platten aufgebrachtes, und im Werkstoff verankertes Textilgewebe, ist es möglich, relativ dünnwandige Innenbehälter vorzufertigen. Durch Aufbringen von

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glasfaserverstärktem Polyesterharz ist es möglich, in sich stabile Behälter herzustellen, die bei entsprechender Auslegung der Druckbehälterverordnung gerecht werden. Im Aufbau weisen diese Behälter folglich eine zweischalige Bauweise auf. Insbesondere handelt es sich dabei um miteinander verbundene Schalen, wobei die innere Schale aus dem erfindungsgemäß ausgewählten HD-Polyethylen besteht und die äußere Schale aus einem

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glasfaserverstärkten Polyesterharz. Weiterhin ist es möglich die Oberfläche der hergestellten Behälter nach dem Fachmann bekannten Methoden zu modifizieren, beispielsweise durch Lackieren, Kaschieren oder Dispersionsbeschichten mittels geeigneter Sperrpolymere oder durch Beschichten mit dünnen Metallfolien. Für diesen Zweck geeignete Sperrpolymere sind Polyamid, Polyester, Polyvinylidendifluorid oder Polymere auf der Basis von Acrylnitril. Auf diese Weise kann die Durchlässigkeit für Gase, Dämpfe und Flüssigkeiten reduziert werden.

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Die in den folgenden Tabellen gegebenen Werte sollen die Erfindung näher verdeutlichen, sind aber nicht dazu geeignet, die Erfindung auf die genannten und untersuchten Polyethylen-Werkstoffe mit der Bezeichnung Lupolen zu beschränken

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Tabelle 1

Freisetzung von kationischen Verunreinigungen aus Polyethylen-Werkstoffen in Gegenwart hochreiner Chemikalien

ermittelte Werte in ng/g Pellet	Lupolen 5021 D 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 6031 M 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 6060 D 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	LLDPE Neste NCPE 8682 1. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C	LLDPE Neste NCPE 8682 2. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C	VEPE Scairlink 8000 G 5 1. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C
Aluminium	16	170	8	218	238	815
Antimon	-	-	-	-	-	-
Arsen	-	-	-	-	-	-
Barium	-	-	-	3	-	3
Beryllium	-	-	-	-	-	-
Wismut	-	-	-	72	84	18
Bor	-	-	-	-	-	-
Cadmium	-	-	-	-	-	-
Kalzium	6,6	60	17	97	110	147
Chrom	4	0,3	45	-	-	-
Kobalt	-	-	-	-	-	-
Kupfer	-	-	-	-	-	-
Gallium	-	-	-	-	-	-
Germanium	-	-	-	-	-	-
Gold	-	-	-	-	-	-

Fortsetzung Tabelle 1:

ermittelte Werte in ng/g Pellet	<b>Lupolen 5021 D</b> 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	<b>Lupolen 6031 M</b> 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	<b>Lupolen 6060 D</b> 1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	<b>LLDPE Neste NCPE 8682</b> 1. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C	<b>LLDPE Neste NCPE 8682</b> 2. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C	<b>VEPE Scairlink 8000 G 5</b> 1. Elution Zeit: 7 Tage Chemikalie: HF 49% 40 °C
Indium	-	-	-	-	-	-
Eisen	18	24	13	52	17	86
Blei	-	-	-	-	-	-
Lithium	-	-	-	-	-	-
Magnesium	1,5	39	-	62	38	82
Mangan	-	-	-	-	-	-
Molybdän	-	-	-	-	-	-
Nickel	-	-	-	-	-	-
Platin	-	-	-	-	-	-
Kalium	3	-	-	30	45	94
Silizium	-	-	-	-	-	-
Silber	-	-	-	-	-	-
Natrium	20	-	16	110	150	300
Strontium	-	-	-	-	-	-
Thallium	-	-	-	-	-	-
Zinn	-	-	-	-	-	1,5
Titan	-	30	-	86	5	16
Vanadium	-	-	-	-	-	3
Zink	0,9	3,6	8	4800	714	72
Zirkonium	-	-	-	-	-	-

Tabelle 2

Freisetzung von kationischen Verunreinigungen aus weiteren  
Polyethylen-Werkstoffen in Gegenwart hochreiner Chemikalien

5	ermittelte Werte in ng/g Pellet	Hostalen GM6255  1. Elution Zeit: 6 Tage Chemikalie: HF 49% 25 °C	Hostalen GM6255  1. Elution Zeit: 26 Tage Chemikalie: HF 49% 25 °C	Lupolen 4261 A Q 135  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 5261 Z Q135  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 5261 Z Q 445  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 6021 D  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C
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15	Aluminium	60	0,5	60	1040	1110	17
	Antimon	-	-	-	-	-	-
	Arsen	-	-	-	-	-	-
20	Barium	1,5	-	-	-	-	-
	Beryllium	-	-	-	-	-	-
	Wismut	-	-	-	-	84	-
25	Bor	-	-	-	-	-	-
	Cadmium	-	-	-	-	-	-
	Kalzium	90	0,8	10	33	45	3,6
30	Chrom	13	1,3	70	110	147	3,6
	Kobalt	-	-	-	-	-	-
	Kupfer	4	-	1,5	-	-	-
	Gallium	-	-	-	-	-	-
	Germanium	-	-	-	-	-	-
	Gold	-	-	-	-	-	-

Fortsetzung Tabelle 2:

ermittelte Werte in ng/g Pellet	Hostalen GM6255  1. Elution Zeit: 6 Tage Chemikalie: HF 49% 25 °C	Hostalen GM6255  1. Elution Zeit: 26 Tage Chemikalie: HF 49% 25 °C	Lupolen 4261 A Q 135  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 5261 Z Q135  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 5261 Z Q 445  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C	Lupolen 6021 D  1. Elution Zeit: 7 Tage Chemikalie: HCL 35% 40 °C
Indium	-	-	-	-	-	-
Eisen	80	2	63	33	33	6,3
Blei	0,5	-	-	-	-	-
Lithium	-	-	-	-	-	-
Magnesium	26	-	1,5	3	4,5	-
Mangan	1,3	-	0,3	-	-	-
Molybdän	-	-	-	-	-	-
Nickel	2	-	1,5	-	-	-
Platin	-	-	-	-	-	-
Kalium	10	-	30	2	1,5	6,3
Silizium	-	-	-	-	-	-
Silber	-	-	-	-	-	-
Natrium	7	-	16	36	24	24
Strontium	-	-	-	-	-	-
Thallium	-	-	-	-	-	-
Zinn	-	-	-	-	-	-
Titan	-	5	2,5	-	-	-
Vanadium	-	-	-	-	-	-
Zink	29	-	1,5	0,3	2,4	-
Zirkonium	-	-	-	-	-	-



## PATENTANSPRÜCHE

1. Verwendung von HD-Polyethylen (HD = high density) zur Herstellung von massiven Lager- und Transportbehältern für hochreine, flüssige Chemikalien für die Elektronikindustrie.
2. Verwendung von HD-Polyethylen zur Herstellung von Auskleidungen von Lager- und Transportbehältern für hochreine, flüssige Chemikalien für die Elektronikindustrie.
3. Verwendung von HD-Polyethylen zur Herstellung des Equipments, insbesondere von Tauchrohren, sowie von Flüssigkeit fördernde Pumpen für Lager- und Transportbehälter für hochreine, flüssige Chemikalien für die Elektronikindustrie.
4. Verwendung nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es sich um Polyethylen mit einer spezifischen Dichte von 0,945 - 0,970 g/cm<sup>3</sup> handelt.
5. Verwendung nach Anspruch 2, dadurch gekennzeichnet, daß es sich bei der Auskleidung des Lager- und Transportbehälters um einen zweischaligen Innenbehälter handelt, dessen innere Schale aus einem HD-Polyethylen hergestellt wird, welche von einer glasfaserverstärkten Außenschale umhüllt wird.
6. Verwendung nach den Ansprüchen 1 - 5, dadurch gekennzeichnet, daß es sich um ein HD-Polyethylen aus der Gruppe Lupolen 6021 D, Lupolen 5021 D, Lupolen 4261 A Q149, und Lupolen 4261 A Q 135 handelt.
7. Lager- und Transportbehälter für hochreine, flüssige Chemikalien für die Elektronikindustrie, hergestellt aus HD-Polyethylen.
8. Auskleidungen für Lager- und Transportbehälter für hochreine, flüssige Chemikalien für die Elektronikindustrie, hergestellt aus HD-Polyethylen.

9. Tauchrohre für die Verwendung in Lager- und Transportbehältern für hochreine, flüssige Chemikalien für die Elektronikindustrie, hergestellt aus HD-Polyethylen.

5 10. Flüssigkeit fördernde Pumpen für hochreine, flüssige Chemikalien für die Elektronikindustrie, hergestellt aus HD-Polyethylen.

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 97/03534

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B65D85/84 B65D90/02 C08L23/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 673 841 A (MAUSER WERKE GMBH) 27 September 1995 see column 1, line 16 - line 25 see column 2, line 8 - line 11 see column 3, line 37 see column 3, line 55 - column 4, line 3; claims ---	1-10
X	DATABASE WPI Section Ch, Week 8939 Derwent Publications Ltd., London, GB; Class A17, AN 89-282988 XP002043714 & JP 01 208 115 A (MITSUBISHI KASEI CORP) , 22 August 1989 see abstract --- -/--	1-10

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

15 October 1997

Date of mailing of the international search report

10.11.97

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Authorized officer

Clemente Garcia, R

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/03534

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 712 711 A (GEERING EMIL J ET AL) 15 December 1987 see column 1, line 35 see column 2, line 33 - line 47; claims ---	1-10
P,X	EP 0 745 538 A (MAUSER WERKE GMBH) 4 December 1996 see column 2, line 38 - line 42 see column 4, line 40 - line 42; claims -----	1,3-7,9

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/03534

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0673841 A	27-09-95	DE 9405113 U JP 8034050 A	26-05-94 06-02-96
US 4712711 A	15-12-87	NONE	
EP 0745538 A	04-12-96	DE 29509003 U DE 29610451 U	31-08-95 19-09-96

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 97/03534

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES  
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## C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie <sup>a</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP 0 673 841 A (MAUSER WERKE GMBH) 27. September 1995 siehe Spalte 1, Zeile 16 - Zeile 25 siehe Spalte 2, Zeile 8 - Zeile 11 siehe Spalte 3, Zeile 37 siehe Spalte 3, Zeile 55 - Spalte 4, Zeile 3; Ansprüche ---	1-10
X	DATABASE WPI Section Ch, Week 8939 Derwent Publications Ltd., London, GB; Class A17, AN 89-282988 XP002043714 & JP 01 208 115 A (MITSUBISHI KASEI CORP) , 22. August 1989 siehe Zusammenfassung --- -/-	1-10

☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN		
Kategorie <sup>a</sup>	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US 4 712 711 A (GEERING EMIL J ET AL) 15.Dezember 1987 siehe Spalte 1, Zeile 35 siehe Spalte 2, Zeile 33 - Zeile 47; Ansprüche ---	1-10
P,X	EP 0 745 538 A (MAUSER WERKE GMBH) 4.Dezember 1996 siehe Spalte 2, Zeile 38 - Zeile 42 siehe Spalte 4, Zeile 40 - Zeile 42; Ansprüche -----	1,3-7,9

**INTERNATIONALER RECHERCHENBERICHT**

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 97/03534

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP 0673841 A	27-09-95	DE 9405113 U JP 8034050 A	26-05-94 06-02-96
US 4712711 A	15-12-87	KEINE	
EP 0745538 A	04-12-96	DE 29509003 U DE 29610451 U	31-08-95 19-09-96





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/44, 31/415</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/16228</b> <b>(43) International Publication Date:</b> 23 April 1998 (23.04.98)
<b>(21) International Application Number:</b> PCT/SE97/01651 <b>(22) International Filing Date:</b> 1 October 1997 (01.10.97)  <b>(30) Priority Data:</b> 9603725-4      11 October 1996 (11.10.96)      SE  <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> LINDBERG, Per [SE/SE]; Gundas Gata 40, S-431 51 Mölndal (SE). PINAS-MASSO, Joan [ES/ES]; 2°-3° piso, Placa Francesc Masia, 8, E-08029 Barcelona (ES). SERRA-CARRERAS, Jordi [ES/ES]; 1°-3° piso, Paseo Pere III, 71ü, E-08240 Manresa (ES). TRO- FAST, Jan [SE/SE]; Vapenkroken 34, S-226 47 Lund (SE).  <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
<b>(54) Title:</b> USE OF AN H <sup>+</sup> , K <sup>+</sup> -ATPase INHIBITOR IN THE TREATMENT OF NASAL POLYPS  <b>(57) Abstract</b> <p>The invention provides a method for the treatment of polyposis which comprises treating a subject suffering from polyposis with an H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor and, optionally, a glucocorticoid. The invention also relates to a pharmaceutical formulation for simultaneous, separate or sequential administration in the treatment of Widal's Syndrome and in the treatment of asthma.</p>		

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USE OF AN  $H^+$ ,  $K^+$ -ATPASE INHIBITOR IN THE TREATMENT OF NASAL POLYPS*Field of the invention*

The present invention provides a new treatment for polyposis using proton pump inhibitors (PPIs), i.e.  $H^+$ ,  $K^+$ -ATPase inhibitors.

5

*Background of the invention*

Polyposis can generally arise in the nose and the gastrointestinal tract. In the nose, polyps are pale bags of tissue that arise in the nasal cavity. Their paleness is generally due to poor blood supply. It is not known what causes the polyps to be formed but their presence is often associated with certain medical conditions, for example asthma and aspirin intolerance. Within the general population the incidence of nasal polyps is low at around only 1% but 13% of asthma sufferers and 36% of aspirin intolerant asthmatics suffer from nasal polyposis. The triple condition of nasal polyposis, aspirin intolerance and asthma is known as Widal's Syndrome.

15

Nasal polyposis is generally treated in two stages. Initially a reduction in size of the polyps is achieved either by surgery or by the application of a topical intranasal steroid preparation, for example betamethasone sodium phosphate. Once a reduction in size has been obtained then long term maintenance of the reduction is necessary by regular use of an intranasal steroid spray such as beclomethasone dipropionate, budesonide, or fluticasone propionate. When rapid amelioration is required, oral steroids such as prednisolone or dexamethasone or synthetic adrenocorticotrophic hormones are used (see V J Lund Diagnosis and treatment of nasal polyps Brit Med J 1995, 311, 1411-4). There are also proposals that non-steroidal antiinflammatory drug can be used in the treatment of nasal polyposis (see WO 9703659-A).

25

*Detailed Description of the Invention*

According to the invention there is provided a method for the treatment of nasal polyps which method comprises treating a subject suffering from the said condition with an  $H^+$ ,

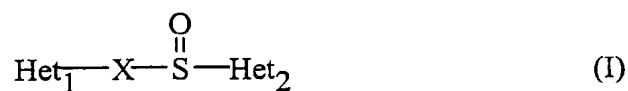
K<sup>+</sup>-ATPase inhibitor. The invention further provides the use of an H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor in the manufacture of a medicament for the treatment of nasal polyps.

H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are a known class of pharmaceutical agents generally used in therapy for the treatment of gastric acid related diseases. Examples of H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Some of these compounds are for instance disclosed in EP-A1-0005129, EP-A1-174726, EP-A1-166287 and GB 2163747.

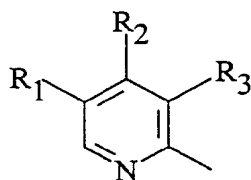
These pharmaceutical substances are generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid secretory pathway. Thus, in a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers.

It has now surprisingly been found that H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors are useful in the treatment of nasal polyps, particularly where known treatments have failed.

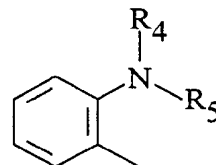
The H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitors preferably used in the invention are compounds of the general formula



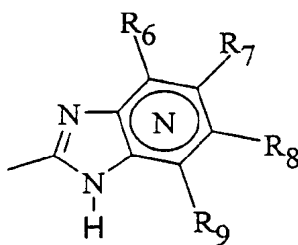
wherein Het<sub>1</sub> is



or

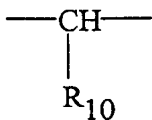


Het<sub>2</sub> is

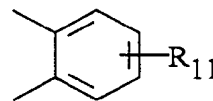


5

and X is



or



wherein N in the benzimidazole moiety of Het<sub>2</sub> means that one of the ring carbon atoms  
 10 substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any  
 substituents;

R<sub>1</sub> and R<sub>3</sub> each independently represent hydrogen, alkyl, or alkoxy on the condition that R<sub>1</sub>  
 and R<sub>3</sub> do not simultaneously represent alkoxy; and R<sub>2</sub> represents alkyl, alkoxy optionally  
 15 substituted by fluorine, alkylthio or alkoxyalkoxy; or one of R<sub>1</sub> and R<sub>3</sub> is halogen and the  
 other is hydrogen and R<sub>2</sub> is 1-morpholino, 1-piperidino or dialkylamino;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen and alkyl;

$R_6$ - $R_9$  are the same or different and selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy, alkylcarbonyl, and alkoxy carbonyl;

- 5  $R_{10}$  is hydrogen or  $R_{10}$  and  $R_3$  together complete a ring containing 6 to 8 carbon atoms;  
and

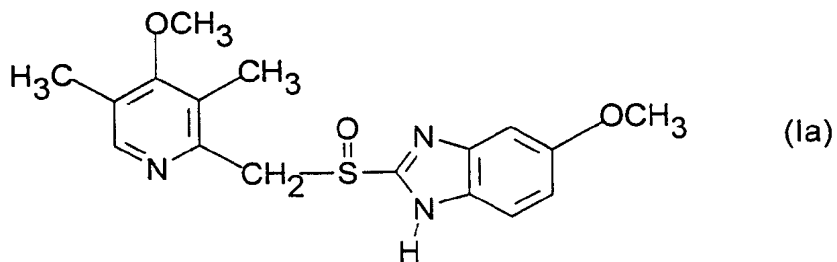
$R_{11}$  represents hydrogen, halogen or alkyl;

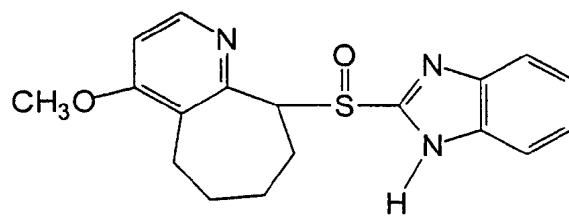
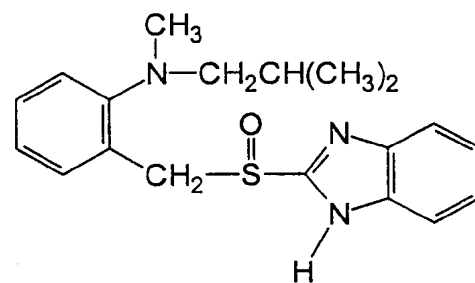
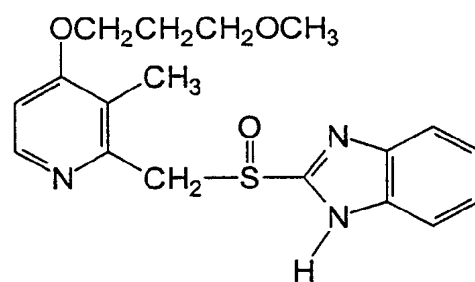
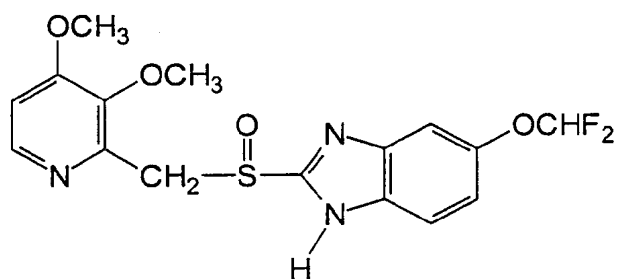
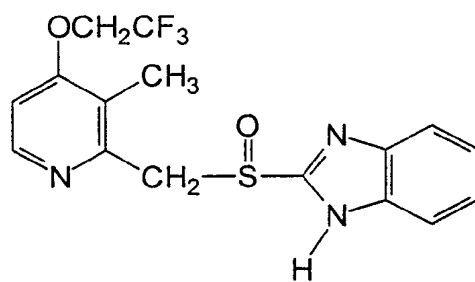
- 10 wherein the compound of formula (I) is optionally in the form of a pharmaceutically acceptable alkaline salt or in its neutral form or is a single enantiomer or a racemic mixture thereof;

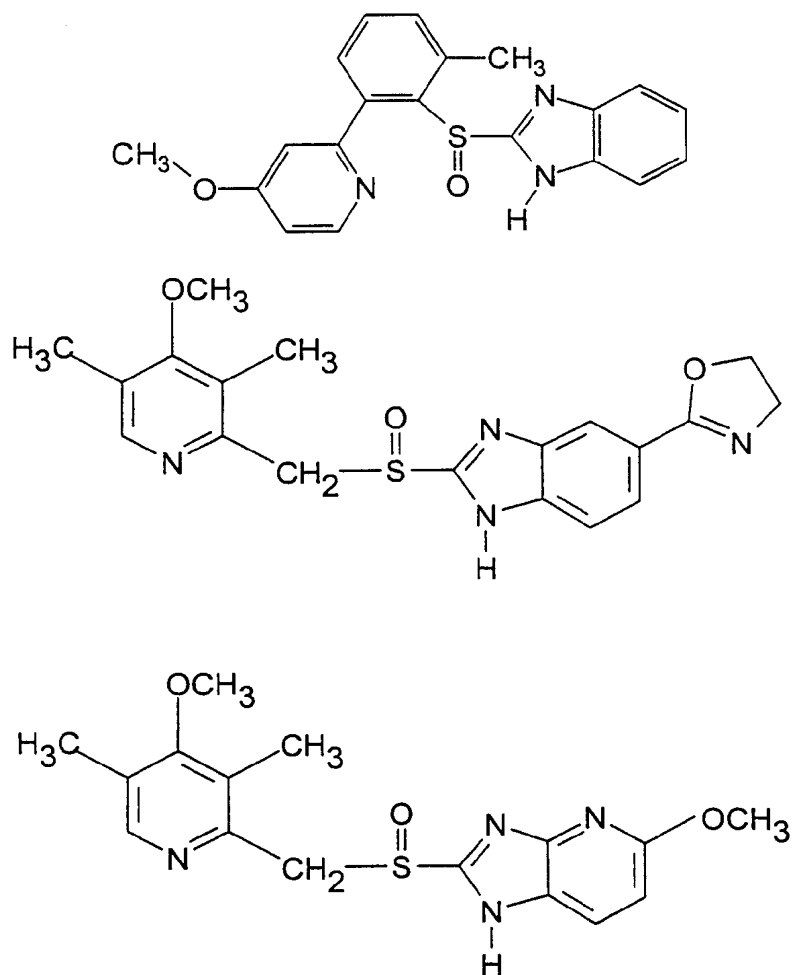
- wherein each alkyl or alkylenyl moiety has a branched or straight chain and has 1 to 6,  
15 preferably 1 to 4, carbon atoms;

wherein a halogen atom is preferably a fluorine, chlorine, or bromine atom, preferably a fluorine or chlorine atom.

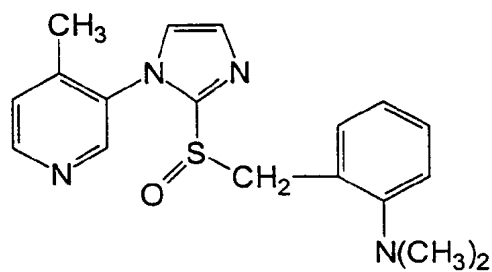
- 20 Examples of particularly preferred compounds according to formula I for use in the invention are







5 and



The  $H^+$ ,  $K^+$ -ATPase inhibitor used in the invention is preferably of formula (Ia): in other words it is preferably omeprazole, or an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole or an alkaline salt thereof.



The compound of formula (I) when optionally in the form of a pharmaceutically acceptable alkaline salt is preferably the  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Na}^{+}$  or  $\text{K}^{+}$  salt, more preferably the  $\text{Mg}^{2+}$  salt.

The  $\text{H}^{+}$ ,  $\text{K}^{+}$ -ATPase inhibitor used in the invention can be administered orally, rectally or parenterally. While the effect of the inhibitors on the nasal polyps has been established in patients who have taken omeprazole by the oral route, it is believed that the effect of the inhibitor on the polyps is a systemic effect that is not dependent on what mode of administration is used. Accordingly a reduction in size of the polyps should be obtainable with other routes of administration.

Commercially available pharmaceutical preparations of  $\text{H}^{+}$ ,  $\text{K}^{+}$ -ATPase inhibitors are suitably used in the invention. Examples of such preparations for omeprazole include enteric coated pellets of omeprazole filled in capsules, or formulated into a multiple unit tableted dosage form; enteric coated tablets of omeprazole or an alkaline salt thereof; and solutions for parenteral administration comprising an alkaline salt of omeprazole.

The dose of the  $\text{H}^{+}$ ,  $\text{K}^{+}$ -ATPase inhibitor to be administered will vary according to the type of nasal polyps to be treated and the condition of the patient. However the dosage for oral, rectal or i.v. administration is generally in the range of from 1 to 100 mg of  $\text{H}^{+}$ ,  $\text{K}^{+}$ -ATPase inhibitor per day. Normally an amount of from 10 to 40 mg per day is used for oral administration.

The invention may be applied in combination with other treatments known to ameliorate the other symptoms generally associated with nasal polyps, for example asthma. In other words, the invention can be applied in the treatment of Widal's Syndrome which consists of the conditions of nasal polyps, asthma and aspirin intolerance. The invention may also be applied in the treatment of other inflammatory diseases in the upper respiratory tract such as acute and chronic rhinosinusitis, allergic and non-allergic rhinitis, as well as in the lower respiratory tract such as asthma. Therefore according to the invention there is further

provided a method for treating Widal's Syndrome and other respiratory tract inflammatory diseases which method comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome or the diseases a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid. According to the invention  
5 there is also provided a pharmaceutical formulation for simultaneous, separate or sequential administration to be used in the treatment of Widal's Syndrome or in the treatment of asthma which formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid. The invention further provides the use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of such a pharmaceutical formulation.

10

Preferred glucocorticoids are topically active anti-inflammatory steroids. Examples of suitable steroids include budesonide; rofleponide; rofleponide palmitate; ciclesonide; mometasone furoate; fluticasone propionate;  $16\alpha$ ,  $17\alpha$ -butylidenedioxy- $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ , 21-dihydroxypregna-1, 4-diene-3, 20-dione;  $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ ,  $17\alpha$ -  
15 dibutylidenedioxy- $17\alpha$ -methylthio-androsta-4-ene-3-one; S-methyl- $16\alpha$ ,  $17\alpha$ -butylidenedioxy- $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy-3-oxo-androsta-1, 4-diene  $17\beta$ -carbothioate; methyl  $9\alpha$ -chloro- $6\alpha$ -fluoro- $11\alpha$ -hydroxy- $16\alpha$ -methyl-3-oxo- $17\alpha$ -propionyloxy-androsta-1, 4-diene- $17\alpha$ -carboxylate;  $6\alpha$ ,  $9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo- $17\alpha$ -propionyloxy-androsta-1,4-diene- $17\beta$ -carbothioic acid S-(2-oxo-  
20 tetrahydro-furan-3S-yl) ester; tipredane; fluocinolone acetonide; flunisolide; flumethasone; dexamethasone; betamethasone; beclomethasone dipropionate; deflazacort; cortivazol; or cortisol and/or hydrocortisol, optionally in their pure isomeric forms (where such forms exist) and in the forms of their pharmaceutically acceptable salts.

25 The steroids for use in the invention may be applied using conventional dosing rates, e.g. 40 to 3000  $\mu g$  per day. Administration may be by inhalation orally or intranasally. The steroids can optionally be adapted to be administered from a dry powder inhaler, a pressurised metered dose inhaler, or a nebuliser.

When the steroids are administered from a pressurised inhaler, they are preferably in micronised form. They are suspended or dissolved in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with other propellants and/or surfactants and/or other excipients, for example ethanol, surfactants, lubricants, anti-oxidants and stabilising agents.

When the steroids are administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The invention is described more in detail with reference to the following examples.

#### *Example 1*

A 53 year old woman who had had Widal's Syndrome for several years but who had refused surgical treatment of her polyps suffered mild upper abdominal pain and no improvement in the polyps after treatment by topical and systemic corticosteroids. However within two weeks of being prescribed 20 mg of omeprazole per day in addition to 100 µg of budesonide (Aqua preparation) per nostril/b.i.d. and 6 mg of deflazacort per day, she experienced a progressive improvement in her nasal respiratory problem. Eventually she recovered completely from the polyps.

#### *Examples 2 to 10*

Nine patients, each with the conditions shown in the following Table 1, were treated during a two week period. The treatment consisted of 20 mg of omeprazole, 100 µg of intranasal budesonide and 3 to 15 mg of oral deflazacort (deflazacort was used in such a small quantity to ensure the patients' compliance). The results are also shown in Table 1.

*Table 1*

Example No.	Condition	Result
2	Widal's Syndrome	Temporary benefit
3	Widal's Syndrome	Positive effect
4	Widal's Syndrome	Positive effect
5	Nasal Polyposis	Long term benefit
6	Nasal Polyposis	No benefit
7	Nasal Polyposis	Positive effect
8	Nasal Polyposis	Positive effect
9	Nasal Polyposis and aspirin intolerance	Positive effect
10	Nasal Polyposis and asthma	No benefit

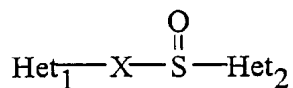
Where a positive effect is indicated, this means that the patient experienced a decrease in rhinorrhoea, a marked improvement in nasal respiratory ventilation and a reduction in the size of the polyps. The patient who experienced a temporary benefit by the treatment suffered a recurrence of the polyposis following the withdrawal of omeprazole and deflazacort (topical anti-inflammatory steroids, i.e. budesonide, were taken as required). However after treatment with the same regimen was resumed, a marked reduction in the size of the polyps was achieved.

10

The patient of Example 5 who experienced a long term benefit initially experienced no benefit at the end of the initial 2 week treatment period but continued with omeprazole and was rewarded with a positive effect at the end of 2 months.

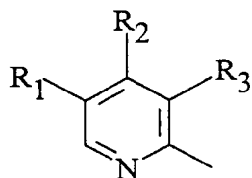
*Claims*

1. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor in the manufacture of a medicament for the treatment of nasal polyps.
2. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor in the manufacture of a medicament for the treatment of Widal's Syndrome.
3. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of a pharmaceutical formulation intended for simultaneous, separate or sequential administration in the treatment of Widal's Syndrome.
4. Use of an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid in the manufacture of a pharmaceutical formulation intended for simultaneous, separate or sequential administration in the treatment of asthma.
5. Use according to claim 3 wherein the glucocorticoid is a topically active anti-inflammatory steroid.
6. Use according to claim 4 wherein the glucocorticoid is budesonide, beclomethasone dipropionate or fluticasone propionate.
7. Use according to any one of the preceding claims wherein the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound of formula

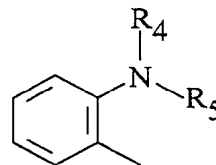
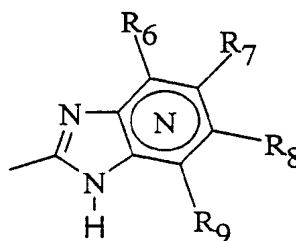


I

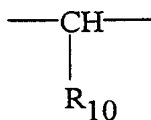
wherein  $\text{Het}_1$  is



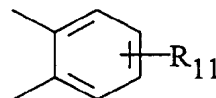
or

Het<sub>2</sub> is

5 and X is



or



wherein N in the benzimidazole moiety of Het<sub>2</sub> means that one of the ring carbon atoms substituted by R<sub>6</sub>-R<sub>9</sub> optionally may be exchanged for a nitrogen atom without any  
 10 substituents;

R<sub>1</sub> and R<sub>3</sub> each independently represent hydrogen, alkyl, or alkoxy on the condition that R<sub>1</sub> and R<sub>3</sub> do not simultaneously represent alkoxy; and R<sub>2</sub> represents alkyl, alkoxy optionally substituted by fluorine, alkylthio or alkoxyalkoxy; or one of R<sub>1</sub> and R<sub>3</sub> is halogen and the  
 15 other is hydrogen and R<sub>2</sub> is 1-morpholino, 1-piperidino or dialkylamino;

R<sub>4</sub> and R<sub>5</sub> are the same or different and selected from hydrogen and alkyl;

R<sub>6</sub>-R<sub>9</sub> are the same or different and selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy, alkylcarbonyl, and alkoxycarbonyl;

R<sub>10</sub> is hydrogen or R<sub>10</sub> and R<sub>3</sub> together complete a ring containing 6 to 8 carbon atoms;

5 and

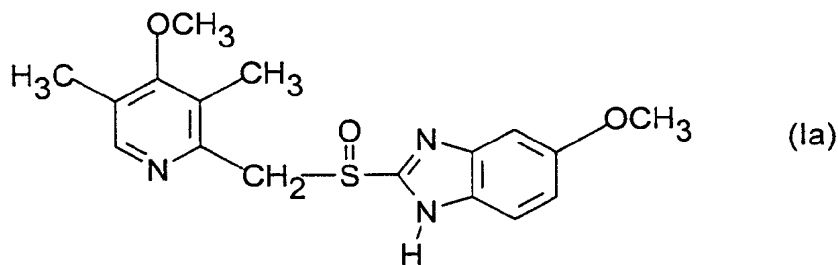
R<sub>11</sub> represents hydrogen, halogen or alkyl;

wherein the compound of formula (I) is optionally in the form of a pharmaceutically  
10 acceptable alkaline salt or in its neutral form or is a single enantiomer or a racemic mixture thereof;

wherein each alkyl or alkylenyl moiety has a branched or straight chain and has 1 to 6 carbon atoms.

15

8. Use according to claim 7 wherein the compound of formula (I) is a compound of formula



20 or an alkaline salt thereof, or the (-)-enantiomer or an alkaline salt of the (-)-enantiomer.

9. A method for the treatment of nasal polyps which method comprises treating a subject suffering from the said condition with a pharmaceutical formulation comprising an H<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor.

25

10. A method for the treatment of Widal's Syndrome which comprises treating a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor.
- 5 11. A method for the treatment of Widal's Syndrome which comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
- 10 12. A method for the treatment of asthma which comprises simultaneously, separately or sequentially administration to a subject suffering from the syndrome with a pharmaceutical formulation comprising an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
13. A method according to claim 11 wherein the glucocorticoid is a glucocorticoid defined in claim 5 or 6.
- 15 14. A method according to any one of claims 9 to 13 wherein the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound of the formula defined in claim 7 or 8.
- 20 15. A pharmaceutical formulation for simultaneous, separate or sequential use in the treatment of Widal's Syndrome which formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
- 25 16. A pharmaceutical formulation for simultaneous, separate or sequential administration in the treatment of asthma which pharmaceutical formulation comprises an  $H^+$ ,  $K^+$ -ATPase inhibitor and a glucocorticoid.
17. A pharmaceutical formulation according to claim 15 or 16 wherein the glucocorticoid is a glucocorticoid defined in claim 5 or 6.



18. A pharmaceutical formulation according to any of claims 15 - 17 wherein the  $H^+$ ,  $K^+$ -ATPase inhibitor is a compound of the formula defined in claim 7 or 8.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/44, A61K 31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J CLIN GASTROENTEROL., Volume 23, No 1, 1996, M.M. YOUSFI et al, "Resolution of a Metaplastic Duodenal Polyp After Cure of Helicobacter pylori Infection" page 53 - page 54  --	1-2,7-8
A	American Journal of Gastroenterology, Volume 91, No 10, 1996, David Johnson, "World literature review" page 2245 - page 2246  --	3-8,15-18
A	US 4199578 A (NEIL A. STEVENSON), 22 April 1980 (22.04.80)  --	3-8,15-18

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

26 February 1998

Date of mailing of the international search report

27 -02- 1998

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4364923 A (PETER B. COOK ET AL), 21 December 1982 (21.12.82)  -- -----	3-8, 15-18

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01651

**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-14  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
A method for treatment of the human or animal body by therapy, see rule 39.1
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept.

Invention 1. Claims 1 directed to the use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor for the manufacture of a medicament for the treatment of nasal polyps.

Invention 2. Claims 2 directed to the use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor for the manufacture of a medicament for the treatment of Widal's Syndrome.

Invention 3. Claims 3-8 and 15-18 directed to a system for simultaneous, separate or sequential use of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor and a glucocorticoid, pharmaceutical compositions and the use thereof in the manufacture of a pharmaceutical formulation.

The special technical features of inventions 1 and 2 are new medical indications of an H<sup>+</sup>,K<sup>+</sup>-ATPase inhibitor. The special technical feature of invention 3 is a pharmaceutical composition comprising two different therapeutically active components which means an absolute product protection irrespective of the use.

Inventions 1 and 2 have been searched together.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

03/02/98

International application No.

PCT/SE 97/01651

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4199578 A	22/04/80	AU 525470 B AU 4210078 A BE 872319 A DE 2851489 A FR 2423218 A,B GB 1571629 A JP 54084022 A	11/11/82 07/06/79 28/05/79 31/05/79 16/11/79 16/07/80 04/07/79
US 4364923 A	21/12/82	AR 196524 A AT 348115 B AT 352973 A,B AU 471577 B AU 5466073 A BE 798458 A CA 994753 A DE 2320111 A,C DK 134923 B,C FR 2182981 A,B GB 1429184 A JP 925800 C JP 49019014 A JP 53001814 B LU 67462 A NL 157797 B NL 7305438 A SE 399642 B,C US 4044126 A US 4414209 A ZA 7302713 A	06/02/74 25/01/79 25/10/79 29/04/76 24/10/74 19/10/73 10/08/76 31/10/73 14/02/77 14/12/73 24/03/76 22/09/78 20/02/74 23/01/78 05/07/73 15/09/78 23/10/73 27/02/78 23/08/77 08/11/83 27/11/74



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 401/12, A61K 31/44</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/28294</b> <b>(43) International Publication Date:</b> 2 July 1998 (02.07.98)
<b>(21) International Application Number:</b> PCT/SE97/02125 <b>(22) International Filing Date:</b> 16 December 1997 (16.12.97) <b>(30) Priority Data:</b> 9604793-1                      20 December 1996 (20.12.96)      SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BOHLIN, Martin [SE/SE]; Kalmgatan 23, S-121 45 Johanneshov (SE). HORVATH, Karol [SE/SE]; Fronhöjdsvägen 54, S-152 56 Södertälje (SE). Von UNGE, Sverker [SE/SE]; Alvägen 4, S-430 33 Fjärås (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> A NOVEL COMPOUND FORM  <b>(57) Abstract</b>  The invention provides S-omeprazole in a neutral form characterised in that it is in a solid state, preferably in a partly crystalline or substantially crystalline state, such as form A or form B. Furthermore, the invention provides processes for the preparation of S-omeprazole and its use in medicine.		

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## A NOVEL COMPOUND FORM

*Field of the Invention*

The invention provides a neutral form of the S-enantiomer of omeprazole which is S-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in  
5 a new physical form, more specifically in a solid state which can be at least partly crystalline, processes for preparing such a form of the S-enantiomer of omeprazole and pharmaceutical compositions containing it.

*Background of the invention*

The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is effective as a gastric acid secretion inhibitor, and is useful as  
10 an antiulcer agent. In a more general sense, omeprazole may be used for prevention and  
15 treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers,  
20 the R-omeprazole and the S-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in neutral form. The (+)-enantiomer of the neutral form and the (-)-enantiomer of the neutral form were found to have the R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are  
25 described in WO 94/27988.

WO 92/08716 discloses R-omeprazole in its neutral form as an amorphous solid in Example 6. Different salts of the single enantiomers of omeprazole are described in WO 94/ 27988. The latter document discloses the preparation of the neutral form of the S-

enantiomer of omeprazole in, for example, Example 10. However, it was obtained in the form of a syrup or oil which is unsuitable for pharmaceutical use because of the difficulty of handling an oil and incorporating it into solid pharmaceutical compositions, especially in a reproducible manner.

5

### *Description of the Invention*

According to the invention there is provided S-omeprazole in a neutral form, i.e. not in the form of a salt, characterised in that the S-omeprazole is in a solid state.

- 10 Neutral S-omeprazole according to the invention is advantageous because it is more stable, easier to handle and store. It is also easier to characterise because it exists in a more well defined state, easier to purify and easier to synthesise in a reproducible manner.

- 15 S-Omeprazole according to the invention can in general be in an amorphous, partly crystalline or substantially crystalline solid state. Preferably it is in a partly crystalline solid state or a substantially crystalline solid state. More preferably it is in either of form A which is a crystalline form or form B which is a less crystalline form.

### *Detailed description of the drawings*

- 20 Figure 1 shows the X-ray powder diffraction pattern of neutral S-omeprazole in form A. Figure 2 shows the X-ray powder diffraction pattern of neutral S-omeprazole in form B.

### *Detailed description of the invention*

- 25 Forms A and B of S-omeprazole in neutral form are characterised by having X-ray powder diffraction patterns having the  $2\theta$  degree angles, d-values and relative intensities given in Table 1.

Table 1

Form A			Form B		
Angle °2θ	d-value, Å	Relative Intensity	Angle °2θ	d-value, Å	Relative Intensity
5.78	15.29	Very strong	5.65	15.64	Strong
9.50	9.30	Weak	9.57	9.23	Medium
9.99	8.85	Weak	13.75	6.44	Medium
11.54	7.66	Weak	15.75	5.62	Medium
12.54	7.05	Weak	16.47	5.38	Medium
16.27	5.44	Strong	19.36	4.58	Weak
17.09	5.19	Strong	21.94	4.05	Weak
18.18	4.88	Weak	24.69	3.60	Weak
18.95	4.68	Strong	25.28	3.52	Weak
20.90	4.25	Medium	27.33	3.26	Weak
21.57	4.12	Medium	29.75	3.00	Very Weak
22.29	3.99	Medium			
23.17	3.84	Weak			
25.22	3.53	Very Weak			
25.90	3.44	Weak			
26.45	3.37	Weak			
27.70	3.22	Very Weak			
29.66	3.01	Very Weak			

More particularly, neutral S-omeprazole in form A is characterised by the X-ray powder diffraction pattern given in Figure 1 and neutral S-omeprazole in form B is characterised by the X-ray powder diffraction pattern given in Figure 2. The X-ray powder diffraction (XRD) patterns in these were obtained in Bragg-Bretano geometry. Since form B is less crystalline and also has peaks in its powder diffractogram which are related to peaks in the diffractogram of form A it is not clear that this is a different crystal form.

The X-ray diffraction analysis was performed according to standard methods, which can be found in e.g. Kitaigorodsky, A.I. (1973), Molecular Crystals and Molecules, Academic Press, New York; Bunn, C.W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L.E. (1974), X-Ray Diffraction Procedures, John Wiley & Sons, New York.

The expression S-omeprazole refers to the fact that it is substantially free of the R-enantiomer, preferably with an enantiomeric excess of 90%, and more preferably 95% e.e.

In a further aspect, the invention relates to processes for the preparation of neutral S-omeprazole in a solid state which comprise

(a) evaporating a solution of neutral S-omeprazole in one or more organic solvents to a highly concentrated solution, adding a further solvent to the highly concentrated solution and evaporating further until solid amorphous neutral S-omeprazole is formed; or

(b) crystallization from a solution of S-omeprazole in one or more organic solvents and optionally water; or

(c) precipitation from a solution of an alkaline salt of S-omeprazole in water and, optionally one or more organic solvents, with a suitable acid.

Process (a) might be further defined by the following aspects. The highly concentrated solution formed in process (a) should not be so concentrated that it is not possible to carry out the second half of the process. After the further evaporation, additional amounts of a further solvent, i.e. a second solvent, may optionally be added and the remaining solvent is evaporated until no more solvent can be removed. This further solvent is preferably one in which neutral S-omeprazole is soluble, but not very soluble, and is more preferably an anti-solvent. The repeated evaporation procedure helps to remove all the initial solvent which

otherwise would prevent the formation of a solid substance. The resulting amorphous precipitate may optionally be further dried, for instance under reduced pressure.

More particularly process (a) may be carried out by dissolving a water soluble salt of S-omeprazole, preferably by using an alkali metal salt (e.g. the potassium or preferably sodium salt) in water and extracting neutral S-omeprazole to a water immiscible solvent or water immiscible solvent mixture (e.g. methylene chloride or toluene, preferably methylene chloride), by decreasing the pH in the water phase, e.g. from about 11, preferably to a pH of from 7 to 10 (e.g. to a pH of from 7 to 8) with a water soluble acid (e.g. aqueous HCl or aqueous acetic acid, preferably diluted acetic acid). The organic phase containing the neutral form of S-omeprazole may be separated from the water phase and solvent evaporated until a highly concentrated solution is formed, preferably leaving 1-2 ml solvent/g of S-omeprazole. A first portion of a further solvent, e.g. iso-octane or n-heptane, is added in an amount of, for example, 5 - 10 ml/g of S-omeprazole. More solvent is evaporated from the resulting mixture until solid amorphous neutral S-omeprazole is formed. Further amounts of a further solvent, e.g. 5-10 ml/g of S-omeprazole, may be added and re-evaporated until no more solvent can be removed. The resulting solid amorphous neutral S-omeprazole may optionally be further dried, for instance under reduced pressure.

Process (b) might be further defined by the following aspects. The solution of neutral S-omeprazole used in the process (b) of the invention can be formed either (i) by dissolution of already isolated neutral S-omeprazole, for instance from process (a) or (ii) it can be the result of a previous step where neutral S-omeprazole is formed by chemical reaction, or (iii) it can be a solution formed by extraction.

Crystallization in process (b) may be induced by decreasing the solubility of S-omeprazole, e.g. by cooling the mixture, by evaporation of some of the solvents or by mixing with, e.g. by adding, some precipitating solvent or anti-solvent. The crystallization may start

spontaneously, but it is preferable to add seeds of the desired form of neutral S-omeprazole. Most preferably seeds of S-omeprazole form A are added.

Suitable solvents, in which neutral S-omeprazole is soluble but not very soluble and which are preferably used for preparing solutions for use in process (b) by dissolution of neutral S-omeprazole, are, for example, ethyl acetate, iso-butanol, isopropanol, methyl isobutyl ketone, acetone, and acetonitrile. Preferably the solvent is ethyl acetate or acetonitrile; most preferably it is ethyl acetate. The preferred amount of organic solvent is 4-10 ml/g of S-omeprazole.

Suitable organic solvents in which neutral S-omeprazole is very soluble which are suitable for use when the solution in process (b) is a reaction solution or obtained by extraction, are, for example, methylene chloride and toluene. Since neutral S-omeprazole is very soluble in these solvents, it can be necessary to use an anti-solvent to induce crystallisation.

A suitable anti-solvent is, for example, iso-octane, acetonitrile or ethyl acetate; preferably it is ethyl acetate or isooctane. Preferably the crystallisation is induced by adding seed crystals, in particular crystals of form A.

Process (c) might be further defined as described below. Process (c) according to the invention is preferably carried out by dissolving a water soluble salt of S-omeprazole in water or a mixture of water and an organic solvent and crystallisation is induced by mixing with, e.g by addition of, a solution of an acid such that the pH of the final solution is still high enough to prevent significant degradation of the product. The organic solvent(s) is preferably a water miscible solvent(s) such as for instance, acetone, acetonitrile or a lower alkyl alcohol. The acid may be, for example, HCl or acetic acid, preferably aqueous acetic acid. The pH of the final solution may be, for example, from 7 to 10, preferably from 7 to 8.

The starting material of process (c) of the invention is preferably a water soluble salt of S-omeprazole, for example an alkali metal salt, particularly a sodium salt. The resulting precipitate of neutral S-omeprazole is generally in a partly crystalline solid state, in particular, in form B.

5

Evaporation of solvents is preferably carried out by vacuum evaporation using, for example a pressure of from 10 to 20 mbar. Mixing, e.g. agitation, is preferable during crystallization. The crystallization should continue for a period to ensure that crystallization is as complete as possible, e.g. from 1 - 15 hours.

10

When the neutral S-omeprazole is crystallized, as in processes (b) and (c), the crystals may be separated from the solution, e.g. by filtration or centrifugation, followed by washing with a washing liquid, preferably a solvent mixture in which the particular form of neutral S-omeprazole has a very low solubility, for example, an anti-solvent. The preferred proportion of washing liquid to product is from 1:1 to 5:1 by weight. The separated neutral S-omeprazole crystals are preferably dried under conditions which avoid degradation of the product, e.g. at +30 to +40 °C, preferably at reduced pressure of e.g. 10 to 20 mbar, for e.g. 10 to 48 hours.

15

Neutral S-omeprazole according to the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. Neutral S-omeprazole according to the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, neutral S-omeprazole may be useful in the treatment of

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psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these.

Any suitable route of administration may be employed for providing the patient with an effective dosage of neutral S-omeprazole according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

According to the invention there is further provided a pharmaceutical composition comprising neutral S-omeprazole according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of neutral S-omeprazole according to the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from a said condition a therapeutically effective amount of neutral S-omeprazole according to the invention.

The compositions of the invention include compositions suitable for peroral or parental administration. The most preferred route is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy, such as tablets, capsules and multiple unit tablets.

The most suitable route of administration as well as the magnitude of a therapeutic dose of neutral S-omeprazole according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrom, such as a need for higher doses than the average patient. Children and patients with liver diseases



generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

- 5 In general, a suitable oral dosage form may cover a dose range from 10 mg to 80 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 20 mg to 60 mg and, especially preferred from 20 mg to 40 mg total daily dose.
- 10 Neutral S-omeprazole according to the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/ 01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.
- 15 The invention is illustrated by the following examples which should not be interpreted as limiting the invention. The best mode to carry out the invention is according to one of the examples giving S-omeprazole form A.

#### *Example 1*

- 20 Sodium salt of S-omeprazole (8g) was dissolved in water (80 ml) at room temperature. Methylene chloride (80 ml) was added and the product was extracted to the organic phase by addition of diluted (4.8 ml, 25% v/v) acetic acid. The mixture was stirred for 5 minutes and then the two phases were allowed to separate. The organic phase was separated off and charged into a round flask. The methylene chloride was evaporated under vacuum
- 25 until a highly concentrated solution containing approximately 1 ml of methylene chloride per 1g of omeprazole was formed. Iso-octane (40 ml) was added and the solvent was evaporated again until an almost dry, amorphous substance was formed. A further amount of iso-octane was added (20 ml) and the slurry was concentrated by evaporation. The solid

material was dried in an oven at 30 °C under reduced pressure overnight to give 6.5 g solid amorphous neutral S-omeprazole.

Examples 2 to 7 inclusive illustrate the preparation of neutral S-omeprazole form A by  
5 recrystallization of the amorphous substance prepared in Example 1.

#### *Example 2*

Amorphous neutral S-omeprazole (0.5 g) was dissolved in ethyl acetate (2g). The solution  
was placed over night in the refrigerator (-20 °C). Crystals were formed spontaneously. The  
10 slurry of crystals obtained was used for seeding in some of the following Examples.

#### *Example 3*

Amorphous neutral S-omeprazole (2 g) was dissolved in ethyl acetate (20 ml) at room  
temperature. The solution was seeded with the crystals obtained in Example 2 and allowed  
15 to crystallize overnight. The crystals obtained were washed with ethyl acetate (2x2 ml) and  
dried at +20 °C in air to give 1.3 g of neutral S-omeprazole form A.

#### *Example 4*

Amorphous neutral S-omeprazole (0.5 g) was dissolved in 2 ml methylene chloride and 4  
20 ml iso-octane was added. The solution was seeded with a small amount of neutral S-  
omeprazole form A. After 4 days crystals were formed. The substance was filtered off and  
washed with iso-octane (1 ml) and dried at room temperature.

#### *Example 5*

25 Amorphous neutral S-omeprazole (5.0g ) was dissolved at room temperature in ethyl  
acetate (40 ml) and a small amount of water (0.5 ml) was added. The solution was seeded  
with crystalline neutral S-omeprazole form A and cooled to 0 °C. The solution was allowed  
to crystallize overnight at 0°C. The resulting crystals were filtered off, washed with ethyl

acetate (3x5 ml) and dried at +40 °C under reduced pressure to give 3.4 g neutral S-omeprazole form A.

### *Example 6*

- 5 Amorphous neutral S-omeprazole (3 g) was dissolved in toluene (9 ml) at room temperature and ethyl acetate (20 ml) was added. The solution was seeded with neutral S-omeprazole form A and was allowed to crystallize at room temperature for about half an hour. Further ethyl acetate was added ( 9 ml) and the solution was allowed to crystallise overnight. Then the slurry was cooled to 0 °C and allowed to crystallise for 20 hours. The  
10 crystals were filtered off, washed with iso-octane (2x5 ml) and dried at +40 °C under reduced pressure giving 2.0 g of neutral S-omeprazole form A.

### *Example 7*

- Preparation of neutral S-omeprazole form A from an extraction solution in methylene  
15 chloride.

- Sodium salt of S-omeprazole (20g) was dissolved in water (200 ml) at room temperature. Methylene chloride (200 ml) was added. The two phase mixture was agitated and aqueous acetic acid (25% v/v, 12.5 ml) was added. The mixture was stirred for 15 minutes and then  
20 the phases were allowed to separate. The methylene chloride solution was charged into a round flask and solvent was evaporated until the dilution was 4 ml methylene chloride per gram of S-omeprazole. 18.9 g of this solution, containing 3 g of S-omeprazole, was added to a round flask. Acetonitrile was added (50 ml) and the solution was seeded with neutral S-omeprazole form A and left overnight. The methylene chloride was evaporated until 22.5  
25 ml solvent remained. The solution was then allowed to crystallize overnight at room temperature. 15 ml of ethyl acetate was added and the resulting mixture filtered. The crystals were washed with ethyl acetate (3x3 ml) and dried at +40 °C under reduced pressure to give 1.0 g neutral S-omeprazole form A.

*Example 8*

Preparation of neutral S-omeprazole form A by crystallization from a solution of S-omeprazole.

- 5 A reaction mixture containing S-omeprazole (1.9 g) in toluene is concentrated by evaporation of toluene until the concentration is 0.71 g/ml toluene. Then ethyl acetate (16ml) is added to the solution. At room temperature the solution is seeded with 0.2 g neutral S-omeprazole form A and cooled to 0°C. The solution was allowed to crystallize overnight at 0°C. The resulting crystals were filtered off, washed with ethyl acetate (2x4ml)  
10 and dried at 30°C under reduced pressure to give 0.89g neutral S-omeprazole, form A.

*Example 9*

Preparation of neutral S-omeprazole form A by re-crystallization.

- 15 Partly crystalline S-omeprazole, form A (5.0 g) was dissolved in 258ml ethyl acetate at 40°C. The solution was cooled to room temperature and the ethyl acetate was slowly evaporated under reduced pressure until 43ml ethyl acetate remained. At room temperature, the concentrated solution was seeded with neutral S-omeprazole form A. The slurry was then cooled to 0°C for 5 hours. Then, ethyl acetate (6.7ml) was added and the resulting  
20 slurry filtered. The crystals were re-slurried in 20ml ethyl acetate, the solvent was filtered off and the crystals dried at 25°C under reduced pressure to give 2.9g neutral S-omeprazole form A.

*Example 10*

- Preparation of neutral S-omeprazole form B by reaction crystallization from a  
25 water/acetone (80/20 % v/v) mixture.

The sodium salt of S-omeprazole (2g) was dissolved in a mixture of water (16ml) and acetone (4 ml). Aqueous acetic acid (25% v/v) was slowly added to the solution in an amount of 0.45 ml which was until the solution had a pH of 10. The resulting slurry was

left overnight at room temperature and the crystals were filtered off and washed with water (3x5 ml), dried at +40 °C under reduced pressure giving 0.9 g neutral S-omeprazole form B.

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*Example 11*

Preparation of neutral S-omeprazole form B by reaction crystallization from a water/acetone (90/10 % v/v) mixture.

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The sodium salt of S-omeprazole (5.2g) was dissolved in water (46.9 ml). Acetone (5.2 ml) was added to the solution. Under vigorous stirring, 3.2 ml of aqueous acetic acid (25% v/v) was slowly added. Crystallization started when the pH reached 10. At the end of the addition the pH was 7. After 3 hours the crystals were filtered off and washed with water (3x 5 ml). The crystals were dried at 40 °C under reduced pressure over night to give 4.4 g partly crystalline neutral S-omeprazole form B.

*Claims*

1. S-Omeprazole in a neutral form characterised in that it is in a solid state.
- 5 2. S-Omeprazole according to claim 1 characterised in that it is in a partly crystalline state.
3. S-Omeprazole according to claim 1 characterised in that it is in a substantially crystalline state.
- 10 4. S-omeprazole according to claim 2 or 3, characterised in that it is in form A.
5. S-omeprazole according to claim 2 or 3, characterised in that it is in form B.
- 15 6. A process for preparing S-omeprazole according to claim 1 which comprises evaporating a solution of neutral S-omeprazole in one or more organic solvents to a highly concentrated solution, adding a further solvent to the highly concentrated solution and evaporating further until solid amorphous neutral S-omeprazole is formed.
- 20 7. A process for preparing S-omeprazole according to claim 6 which further comprises dissolving an alkaline salt of S-omeprazole in water, extracting neutral S-omeprazole to an organic solvent, by decreasing the pH in the water phase with a water soluble acid, whereafter the organic phase comprising the neutral S-omeprazole is separated from the water phase and further processed by evaporation.
- 25 8. A process for preparing S-omeprazole according to any of claims 1-5 which comprises crystallization from a solution of neutral S-omeprazole in one or more organic solvents and optionally water.

9. A process according to claim 8, wherein the solution of neutral S-omeprazole is formed from dissolving an isolated S-omeprazole in the organic solvent(s).

10. A process according to claim 8 wherein the organic solvent is ethyl acetate or acetonitrile.

11. A process according to claim 8, wherein the solution of neutral S-omeprazole is formed from a chemical reaction solution comprising S-omeprazole in an organic solvent.

12. A process according to claim 8, wherein the solution of neutral S-omeprazole is formed from an extraction phase comprising S-omeprazole in an organic solvent.

13. A process according to claim 11 or 12, wherein the organic solvent is methylene chloride or toluene.

14. A process according to claim 13, further comprising addition of an anti-solvent, such as ethylacetate or isooctan.

15. A process for preparing S-omeprazole according to any of claims 1-5 which comprises precipitation from a solution of an alkaline salt of S-omeprazole in water and, optionally one or more organic solvents, with a suitable acid.

16. A process for preparing S-omeprazole according to claim 15 wherein the alkaline salt of S-omeprazole is dissolved in a mixture of water and an organic solvent.

17. A process according to claim 15, wherein the acid gives a pH in the final solution between 7 and 10.

5 18. S-Omeprazole according to claim 2, 3, 4 or 5 for use in therapy.

19. A pharmaceutical composition comprising S-omeprazole according to claim 2, 3, 4 or 5 as active ingredient in association with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

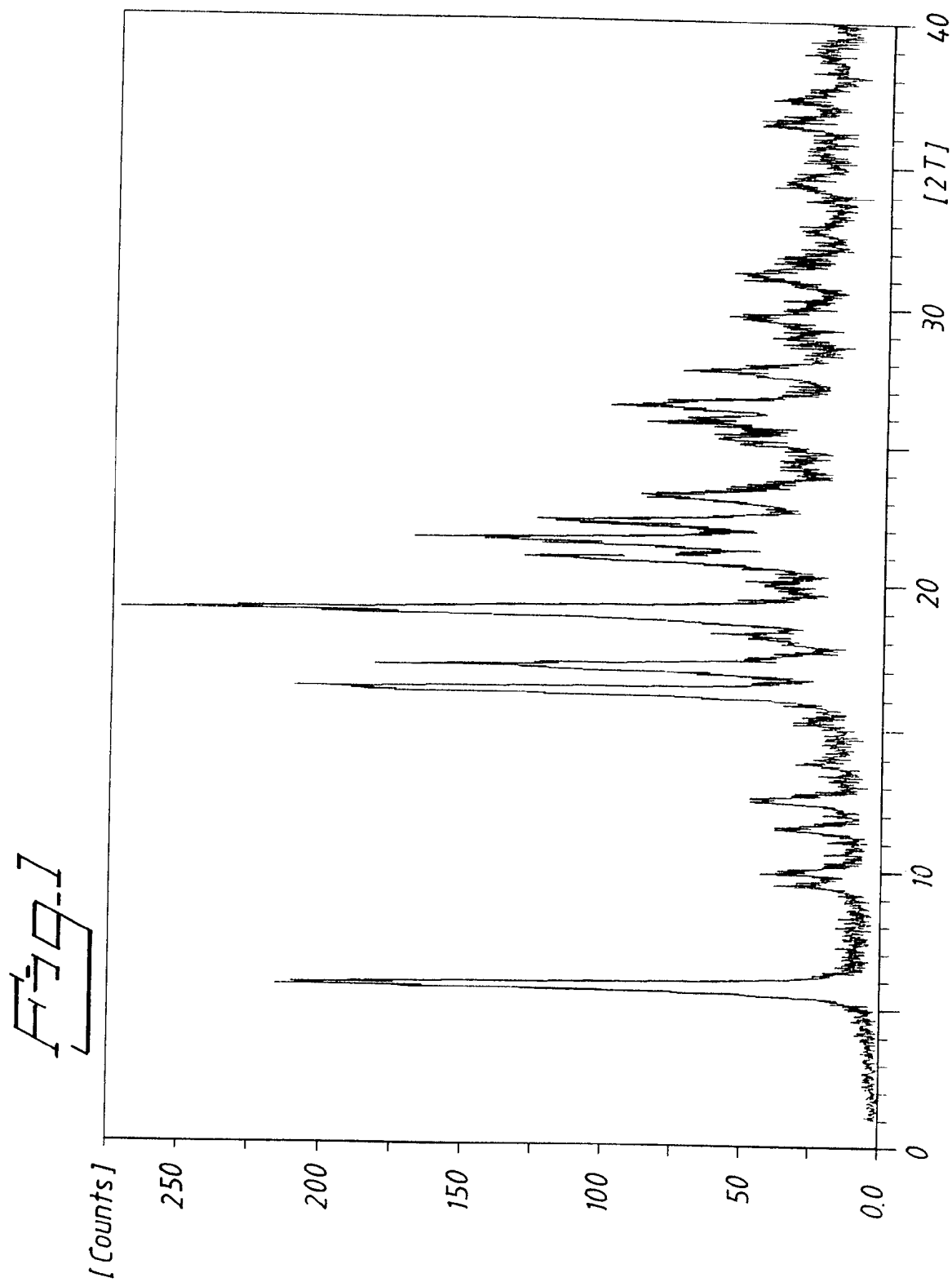
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20. Use of S-omeprazole according to claim 2, 3, 4 or 5 in the manufacture of a medicament for use in the treatment of a gastric-acid related condition.

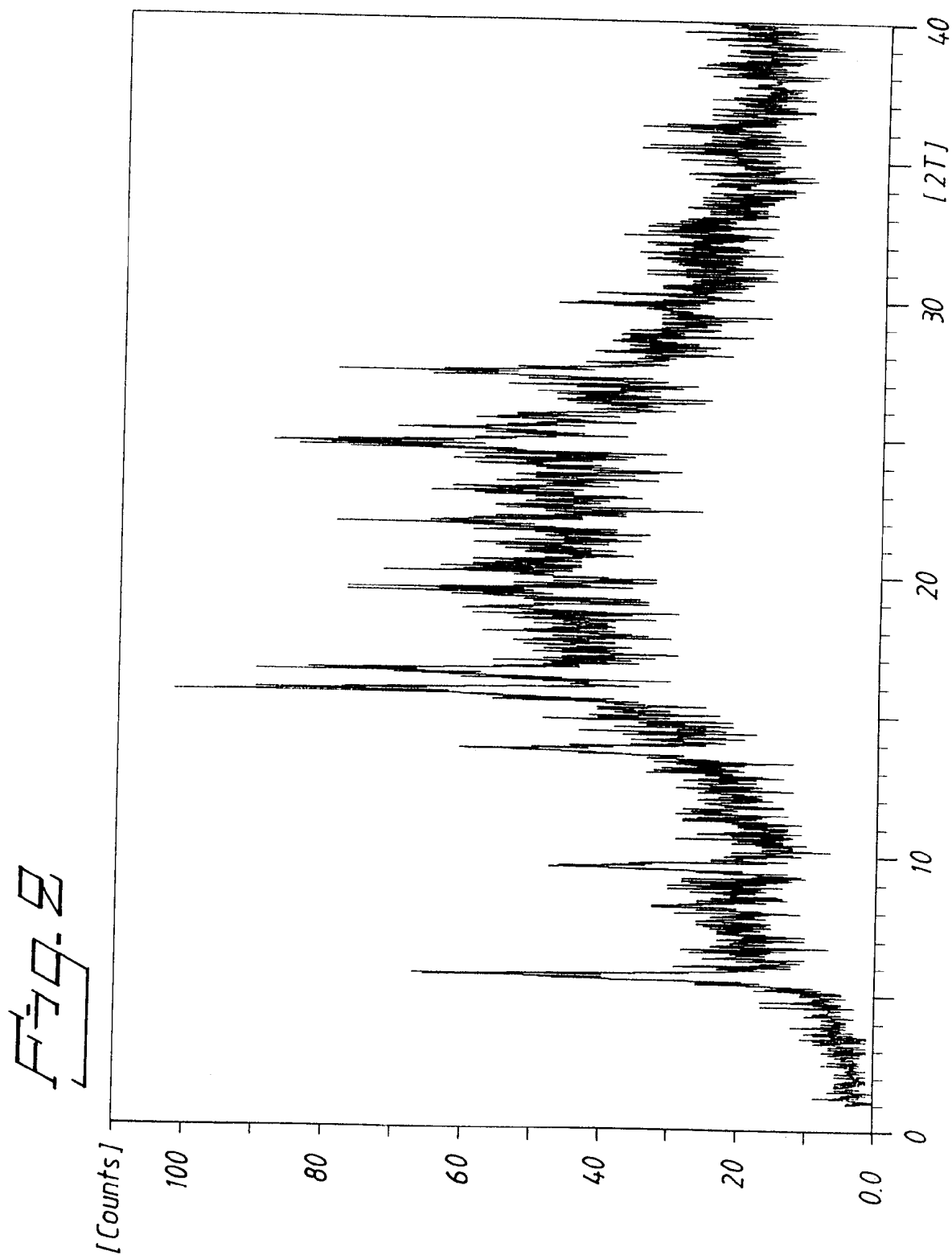
21. A method of treating a gastric-acid related condition which method comprises  
15 administering to a subject suffering from a said condition a therapeutically effective amount of S-omeprazole defined in claim 2, 3, 4 or 5.



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/02125

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9208716 A1 (BYKGULDEN LOMBERG CHEMISCHE FABRIK GMBH), 29 May 1992 (29.05.92), see example 6 and page 9	1,6-7,15-17
A	--	2-4,8-14, 18-20
A	Journal of Chromatography, Volume 532, 1990, Per Erlandsson, "Resolution of the enantiomers of omeprazole and some of its analogues by liquid chromatography on a trisphenylcarbamoylcellulose-based stationary phase. The effect of the enantiomers of omeprazole on gastric glands", page 305 - page 319, see pages 217 - 318	1-20
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

13 March 1998

02-04-1998

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/02125

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.94), see example 10  -----	1-20

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE97/02125

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy, see rule 39.1
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

02/03/98

International application No.

PCT/SE 97/02125

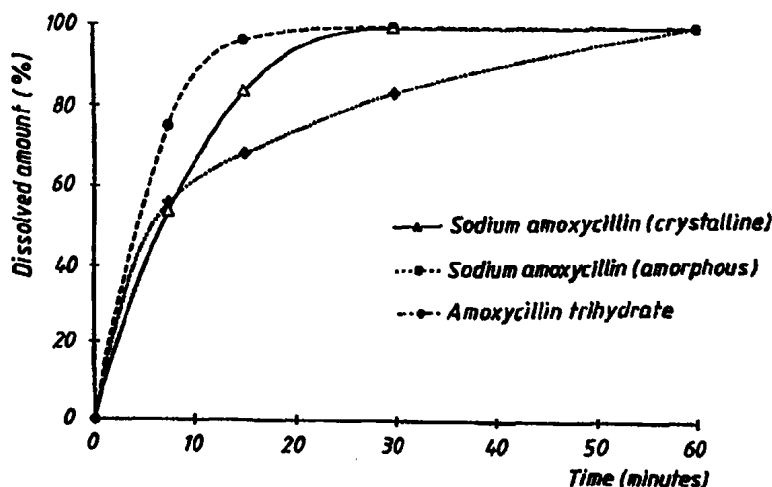
Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9208716	A1	29/05/92	AU	8840691 A	11/06/92
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WO	9427988	A1	08/12/94	AU	676337 B	06/03/97
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				LT	1941 A	27/12/94
				LT	3287 B	26/06/95
				LV	11034 B	20/10/96
				NO	950263 A	24/01/95
				NZ	266915 A	28/10/96
				PL	307261 A	15/05/95
				SI	9420002 A	31/08/95
				SK	10195 A	13/09/95
				US	5693818 A	02/12/97
				US	5714504 A	03/02/98
				ZA	9403557 A	11/04/95
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 9/28, 9/52, 31/44</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/40054</b> (43) International Publication Date: 17 September 1998 (17.09.98)
(21) International Application Number: PCT/SE98/00356 (22) International Filing Date: 27 February 1998 (27.02.98) (30) Priority Data: 9700885-8 12 March 1997 (12.03.97) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): WENDSJÖ, Stig [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report.

(54) Title: AN ENTERIC COATED ORAL DOSAGE FORM COMPRISING SODIUM AMOXYCILLIN

*In vitro* Dissolution of Amoxycillin*pH 5.90; phosphate buffer ( $\mu = 0.1$ ); 100 r.p.m.; stationary basket*

## (57) Abstract

An enteric coated oral dosage form comprising sodium amoxycillin, wherein the dosage form is a single unit tableted dosage form or a multiple unit tableted dosage form is claimed. Processes for the manufacture of the dosage forms as well as the formulations, use in the treatment of *Helicobacter pylori* infections are claimed.

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## AN ENTERIC COATED ORAL DOSAGE FORM COMPRISING SODIUM AMOXYCILLIN

**Field of the Invention**

5 This invention relates to new formulations of sodium amoxycillin, in particular enteric coated oral dosage formulations of sodium amoxycillin, processes for their manufacture and their use in the treatment of *Helicobacter pylori* infections.

**Background of the Invention**

10

The relationship between gastrointestinal disorders and infections and *Helicobacter pylori* (*H. pylori*) was first proposed in 1983 by Warren in The Lancet (1983) 1, 1273. A clear link has now been established.

15 Recently a panel convened by the US National Institute of Health (NIH) has recommended complete eradication of *H. pylori* for those patients with peptic ulcer diseases who are infected with the bacterium. Therapies which have been proposed in this regard include combinations of antibacterial compounds; combinations of a bismuth compound and antibacterial compounds (see for example International Patent Application WO 89/03219);  
20 combinations of ranitidine and antibacterial compounds; and combinations of proton pump inhibitors with antibacterial compounds (see for example International Patent Applications WO 93/21920 and WO 92/03135).

In these proposed combination therapies each single active substance is administered  
25 separately in different dosage forms. However, administration of two or more different tablets is not typically seen as convenient or satisfactory by the patient and therefore such therapy has the disadvantage of poor patient compliance and therefore poor results.

Thus, in order to limit the problem of poor patient compliance in the treatment of *H. pylori*  
30 infections, there is a need for an effective single dosage unit comprising two or more of the above active ingredients.

In the treatment of *H. pylori* infections with antibacterial agents acting via the systemic circulation - whether this is in combination with one or more of the above active agents or otherwise - it is desirable to ensure that release of active substance(s) takes place in the small intestines where the systemic circulation is known to occur. This is because the topical effects of antibacterial agents on *H. pylori* are known to be limited when compared to systemic circulation. See R.J. Adamek et al, Am. J. Gastroenterol., 88 (5), (1993), 792-793. Accordingly, it is desirable to produce the highest possible concentration of antibacterial agent in the serum in order to eradicate infection.

The antibacterial agent amoxycillin has been known for many years to be useful in the treatment of wide variety of infections, ranging from bronchitis to urinary-tract infections.

In the treatment of peptic ulcer patients infected with the *H. pylori*, amoxycillin has been indicated as being a preferred antibacterial agent. For example, combination therapies comprising coadministration of omeprazole and amoxycillin have been approved by regulatory authorities in e.g. the United Kingdom and Sweden.

Amoxycillin is typically administered in two forms, amoxycillin trihydrate which is typically administered orally and sodium amoxycillin which is typically administered by injection. Thus, a tablet formulation typically comprises amoxycillin trihydrate and the injection is a solution of sodium amoxycillin.

Although oral formulations of sodium amoxycillin have been reported (see e.g. International Patent Application WO 94/00112), at present none are presently commercially available.

Enteric coated formulations comprising sodium amoxycillin are not previously known at the knowledge of the Applicant.

We have found that, in the treatment of *H. pylori* infections, the above problems may be solved by providing an enteric coated formulation of sodium amoxycillin which may be used as a single therapy or in a combination therapy.

## 5    **Brief Description of the Invention**

According to the invention there are provided enteric coated oral dosage forms comprising sodium amoxycillin (hereinafter referred to as “the dosage forms according to the invention”).

10

Enteric coatings are well known in the art of drug formulation as an effective method of preventing the release of pharmaceutically active agents in the stomach, but which will dissolve and release drug in the small intestine. They are typically used to prevent the release of drugs which are inactivated by the stomach's contents (e.g. pancreatin and erythromycin) or which irritate the gastric mucosa (e.g. aspirin, i.e. acetyl salicylic acid).

15

We have found that sodium amoxycillin exhibits a surprisingly high dissolution rate at pH values typically experienced in the small intestine when compared to amoxycillin trihydrate and that the dosage forms according to the invention comprising exhibit significantly higher maximum serum concentrations. Thus enhanced eradication of *H. pylori*, when compared with conventional formulations of amoxycillin trihydrate, are experienced with an enteric coated formulation of sodium amoxycillin.

20

The present invention relates to an enteric coated oral dosage form providing a fast release of sodium amoxicillin after passage of the stomach and thus a high plasma concentration of amoxicillin and which dosage form in combination with a proton pump inhibitor provides an enhanced eradication of *H. pylori*.

25

## Brief Description of Drawings

Figure 1 shows the result of *in vitro* dissolution test of tablets.

## 5 Detailed Description of the Invention

The dosage forms according to the invention may be formulated as a single unit or as a multiple unit tableted dosage form.

10 Unless otherwise stated or indicated the term "single unit" denotes that the tablet matrix contains the active substance homogenously distributed beneath the surface area and the term "multiple unit" denotes that the active substance is present in the tablet in several units (of which each one may have its own protective surface layer). In both cases the tablet may contain either one single active substance or one or more additional active  
15 substances.

When the dosage form according to the invention is a single unit, sodium amoxycillin may be formulated as a solid granulation along with inactive excipients and compressed into a single unit tablet, prior to application of the enteric coating.

20

Examples of inactive excipients which may be used include diluents, binders, lubricants and, if necessary, wetting agents.

Examples of suitable diluents include lactose, sucrose, dextrose, starches (e.g. sodium starch glycolate, corn starch) cellulose derivatives (e.g. low substituted hydroxypropyl  
25 cellulose, microcrystalline cellulose), mannitol, crosslinked polyvinyl pyrrolidone, microcrystalline and colloidal anhydrous silicon dioxide (Aerosil<sup>®</sup>).

The dry mixture of sodium amoxycillin may subsequently be mixed with a binder, for  
30 example polyvinyl pyrrolidone, hydroxypropyl cellulose, sorbitol and gelatin.

Suitable lubricants which may be employed for the tableting process include for example sodium stearyl fumarate, magnesium stearate and talc.

- 5    Suitable wetting agents include for instance sodium lauryl sulphate dissolved in distilled water.

Sodium amoxycillin may be dry mixed with the appropriate excipients and then tableted, or the mixture may be wet massed with a granulation liquid. The wet mass is dried,  
10    preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for tableting. The tablets are enteric coated in a suitable equipment.

When the dosage form according to the invention is a tableted multiple unit dosage form, the enteric coated pellets, or granules, comprising sodium amoxycillin are prepared as  
15    hereinbefore described for tablets. The enteric coated pellets are mixed with tablet excipients such as fillers, binders, disintegrants and lubricants, and the dry mixture is then compressed into a multiple unit tableted dosage form.

In order to improve the stability of certain dosage forms according to the invention, the  
20    solid tableted granulation or the prepared pellets may optionally be coated with at least one separating layer before application of the enteric coating.

Examples of materials which may be used as a separating layer include pharmaceutically acceptable compounds such as sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl  
25    alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers or mixtures thereof.

The separating layer may further comprise additives such as plasticizers, colorants,  
30    pigments, fillers anti-tacking and anti-static agents, such as magnesium stearate, titanium dioxide, talc or mixtures thereof.

Separating layers may be applied to the prepared tablets or pellets by coating or layering procedures in suitable equipment, such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an  
5 alternative the separating layers may be applied to the tablets or pellets by using a powder coating technique.

The separating layer, when applied, may be of a variable thickness. The maximum thickness of the separating layer is normally only limited by processing conditions.

10 The separating layer may further serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer may be further strengthened by introducing into the layer one or more substances chosen from a group of compounds often used in antacid formulations, for example magnesium oxide, hydroxide or carbonate,  
15 aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds (e.g.  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$  or  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ ), aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable  
20 organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer and thereby strengthen the diffusion barrier.

The separating layer may alternatively be formed *in situ*, for example by reaction of an enteric coating polymer layer with an alkaline reacting compound contained in the tablets  
25 or pellets, upon application of the enteric coating onto the tablets or pellets.

Enteric coatings which may be employed include those known to those skilled in the art, for example cellulose acetate phthalate, acrylate polymers (e.g. acrylic resins such as Eudragit L and Eudragit S), hydroxypropyl methylcellulose phthalate, polyvinyl acetate  
30 phthalate, methacrylic acid copolymers, hydroxypropyl methylcellulose acetate succinate,

polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or combinations thereof.

5 The enteric coating layers may also contain appropriate quantities of pharmaceutically acceptable plasticizers in order to obtain the desired mechanical properties (e.g. flexibility and hardness). Suitable plasticizers include triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or combinations thereof.

10 The amount of plasticizer will depend upon the nature of the constituents of the enteric coating layer formula and how much of the said formula is to be applied to the pellets. Ideally the mechanical properties should be adjusted so that the acid resistance of the enteric coated pellets does not significantly alter during compression of pellets into tablets. Typical amounts of plasticizer are above 10% by weight of the enteric coating layer polymer(s), preferably 15 - 50% and more preferably 20 - 50%.

15 Further additives which may be employed in the enteric coating layer include dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate or -methylethylmethacrylate), anti-tacking and anti-foaming agents. Other compounds may be added to increase film thickness of the enteric coating layer.

20 The film thickness of the enteric coating layer is preferably at least 10  $\mu\text{m}$ , preferably more than 20  $\mu\text{m}$ .

25 Enteric coated pellets may be coated further with one or more over-coating layers in order to prevent agglomeration of pellets and to protect the enteric coating layer from cracking during the compaction process, i.e. the compression of the pellets into a tablet.

30 The over-coating layers may be applied to the enteric coated pellets by coating or layering procedures using suitable equipment such as a coating pan, a coating granulator or in a fluidized bed apparatus, using water and/or organic solvents for the coating or layering process.

Suitable materials for use as the over-coating layers include sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium or combinations thereof.

The overcoating layer may further comprise additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the over-coating layer. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

The prepared single unit tablet or compressed multiple unit tablet is optionally covered with at least one film-forming agent in order that the tablets obtains a smooth surface and to further enhance the stability of the tablets during packaging and transport. Such a tablet coating layer may further comprise additives such as anti-tacking agents, colorants and pigments.

According to further aspects of the invention there are provided processes for the manufacture of a single unit or a multiple unit dosage form according to the invention.

The dosage forms according to the invention are especially advantageous in the treatment of *H. pylori* infections. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and depends upon various factors including the individual requirements of the patient, the mode of administration and the disease state to be treated. In general each dosage form will comprise an amount of sodium amoxycillin corresponding to 50 mg to 2.0 g, preferably 100 mg to 1.0 g amoxycillin.



According to a further aspect of the invention there is provided the use of sodium amoxycillin in the manufacture of an enteric coated oral dosage form for use in the treatment of *H. pylori* infections.

5 The dosage forms according to the invention may be administered alone or in combination with proton pump inhibitors. Any compound which is known in the art and indicated as being a proton pump inhibitor may be used in conjunction with the dosage forms according to the invention. Proton pump inhibitors may be used in any form (e.g. in the none-salt form or as an alkali or an alkaline earth metal salt). Examples of suitable proton pump  
10 inhibitors include those described in European Patent Applications EP 0 005 129, EP 1 174 726 and EP 1 166 287; United Kingdom Patent Application GB 2 163 747; and International Patent Applications WO 90/06925, WO 94/27988 and WO 95/01977. Particular proton pump inhibitors which may be mentioned include omeprazole, lansoprazole, pantoprazole, pariprazole (rabeprazole) and limoprazole or its single  
15 enantiomers. Of particular interest is omeprazole, S-omeprazole or an alkaline salt thereof.

Proton pump inhibitors may be coadministered separately along with the dosage forms according to the invention. However, in order to eliminate the problems of poor patient compliance mentioned hereinbefore we prefer that the dosage form further comprises a  
20 proton pump inhibitor, i.e. that the sodium amoxycillin and proton pump inhibitor are coformulated in an enteric coated oral dosage form.

Coformulation of proton pump inhibitors and sodium amoxycillin into an enteric coated oral dosage form may be carried out in accordance with known techniques, such as those  
25 described hereinbefore and/or those described in International Patent Application WO 96/01623.

Alternatively the dosage forms according to the invention may be administered in combination with another gastric acid suppressing agents, such as a H<sub>2</sub>-receptor antagonist,  
30 for instance ranitidine, cimetidine or famotidine.

The dosage forms according to the invention may further be administered in combination with other antibacterial agents. Antibacterial agents which may be mentioned include for example nitroimidazole antibiotics, tetracyclines, penicillins, cephalosporins, carbopenems, aminoglycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. Examples of antibacterial compounds are: ampicillin, amoxicillin trihydrate, benzylpenicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, peperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalixin, cefaclor, cedadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol.

The dosage forms according to the invention have the advantage that they are especially advantageous in the treatment of *H. pylori* infections, for example as shown in the tests described below.

The dosage forms according to the invention may also have the advantage that they are less toxic than, are more easily prepared than, produce less side effects than, have a longer shelf-life than, increase the stability of the pharmaceutically active compound more than, or have other useful pharmacological properties over, similar dosage forms which are known in the prior art.

## Tests

### Test A

#### 5 *In vitro* Dissolution

Discs having a diameter of 11.3 mm were compressed of different substances in a Diaf excenter press using flat faced table punches. The discs were centrically mounted on a round steel plate with hollow fitting for the discs. The discs were attached to the steel plate using a water resistant tape with a circular hole of 0.50 cm<sup>2</sup>. The steel plate and the disc  
10 were attached to a motor (IKA RW20 DZM). While rotating, the disc was lowered into 200 ml of buffer pH 5.9 thermostated at 37°C. The rotating velocity was 500 rpm. At each run, the dissolution medium was analysed by continuous recirculation through the spectrophotometer using a 10 mm flow cuvette and a peristaltic pump.

15 Concentrations in the dissolution medium were determined spectrophotometrically using a Perkin Elmer Lambda 2 spectrophotometer. The pH values were measured using a Metrohm 620 pH-meter.

The observed dissolution rates, G, measured as (mg)/(cm<sup>2</sup> . s) were calculated by linear  
20 regression analysis of the amount of drug dissolved per cm<sup>2</sup> as a function of time.

### Test B

25 Urea breath test or Urease biopsy test were used to show activity for *Helicobacter pylori*.

The invention is illustrated, but in no way limited, by the following examples.

## Examples

### Example 1: Dissolution test of tablets

The *in vitro* dissolution (Test A) of sodium amoxycillin (lyophilised), sodium amoxycillin  
5 (crystalline) and amoxycillin trihydrate was determined in a buffer solution at pH 5.9  
( $\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$ ; ionic strength = 0.1  $\mu$ ).

The dissolution rates from centrically mounted discs prepared from the different  
substances, as described in Test A, are shown in Figure 1. The dissolved amounts were  
10 normalized to 100% dissolution after 60 minutes.

The dissolution rate of amoxycillin sodium is 100 times faster than for amoxycillin  
trihydrate. No difference of the dissolution rate between lyophilised and crystalline  
amoxycillin sodium was observed.

15

### Example 2: Preparation of enteric coated tablets comprising sodium amoxycillin

Sodium amoxycillin 224 g  
corresponds to 200 g amoxycillin  
20 Microcrystalline cellulose 245 g  
Sodium starch glycolate 75 g  
Polyvinylpyrrolidone 38 g  
Magnesium stearate 8.4 g

25 Sodium amoxycillin was mixed in a planetary mixer for 5 minutes with microcrystalline  
cellulose and sodium starch glycolate. The resultant mixture was then moistened for 5  
minutes with a solution of polyvinylpyrrolidone in isopropanol and dried. The granulate  
was milled through a 1.0 mm sieve and lubricated for 2 min with magnesium stearate.

The granulate was compressed to tablets on a tableting machine fitted with 12 mm punches. Each tablet contained an amount of sodium amoxicyllin corresponding to 200 mg amoxycillin.

- 5 The obtained tablets are covered with a separating layer and an enteric coating layer.

Solution for separating layer (for 10 kg tablets)

- Hydroxypropyl methylcellulose 300 g  
10 Hydrogen peroxide (30%) 0.003 g  
Water purified 2700 g

Solution for enteric coating layer (for 10 kg tablets)

- 15 Methacrylic acid copolymer dispersion (30%) 2450 g  
Polyethylene glycol 400 80 g  
Titanium dioxide 100 g  
Water purified 1960 g

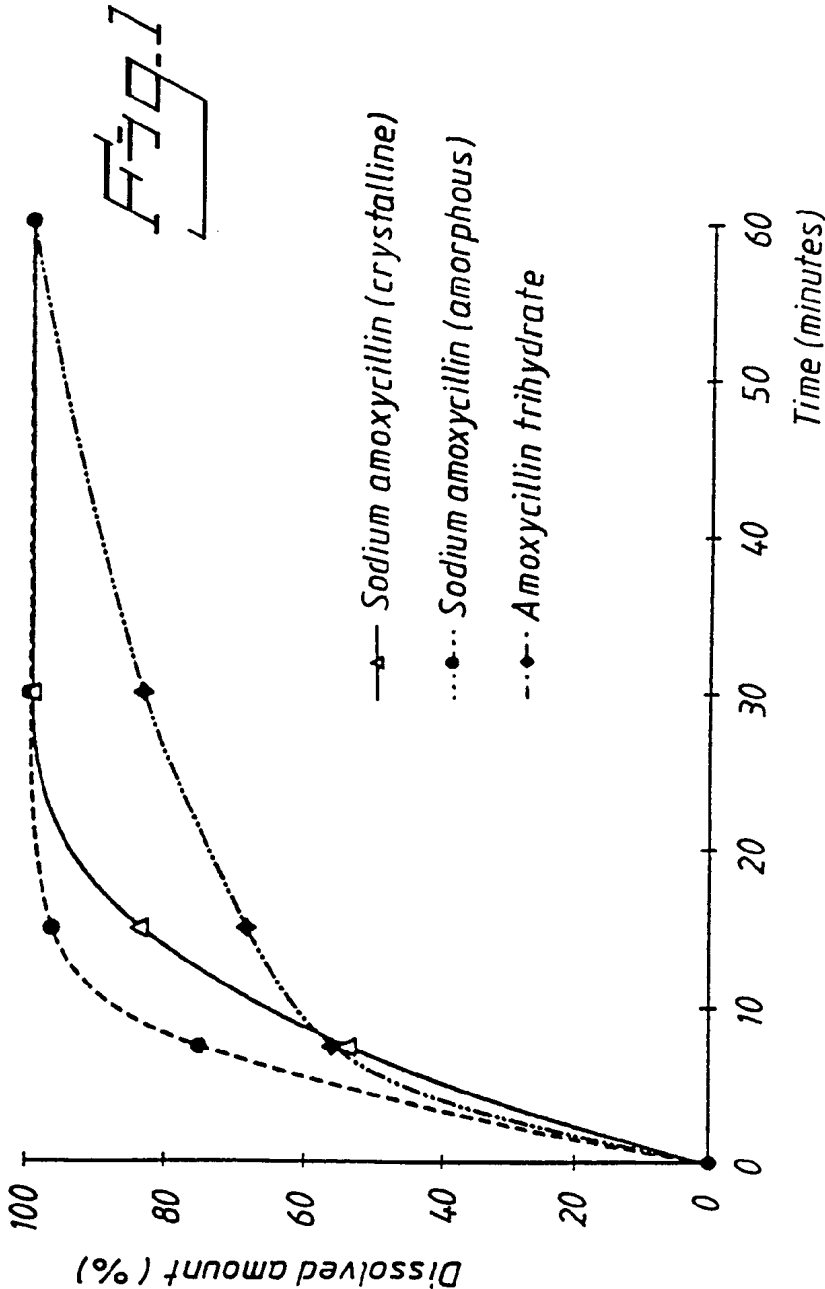
**Claims**

1. An enteric coated oral dosage form comprising sodium amoxycillin.
- 5 2. A dosage form as claimed in claim 1, characterised in that the dosage form is a single unit tableted dosage form.
3. A dosage form as claimed in claim 1, characterised in that the dosage form is a multiple unit tableted dosage form.
- 10 4. A dosage form according to claim 3, characterised in that the dosage form comprises individually enteric coated pellets comprising sodium amoxycillin, and the enteric coated pellets and tablet excipients are compressed into a tablet.
- 15 5. A dosage form as claimed in any one of claims 1 to 4, characterised in that the sodium amoxycillin is amorphous.
6. A dosage form as claimed in any one of claims 1 to 5 in combination with a dosage form comprising a proton pump inhibitor.
- 20 7. A dosage form as claimed in any one of claims 1 to 5 which further comprises a proton pump inhibitor.
8. A dosage from as claimed in claim 7, characterised in that the proton pump inhibitor is  
25 omeprazole, S-omeprazole or an alkaline salt thereof.
9. The use of sodium amoxycillin in the manufacture of an enteric coated oral dosage form.
10. A process for the manufacture of an enteric coated single unit dosage form comprising  
30 sodium amoxycillin, characterised in that sodium amoxycillin is mixed with tablet

excipients, compressed into a tablet and the tablet is coating layered with an enteric coating.

11. A process for the manufacture of an enteric coated oral dosage form comprising a  
5 multiplicity of enteric coated pellets of sodium amoxycillin, characterised in that sodium  
amoxycillin is mixed with pharmaceutically acceptable excipients, the mixture is  
formulated into pellets, the pellets are coating layered with an enteric coating, the coated  
pellets mixed with tablet excipients and compressed into a tablet.
- 10 12. A process according to any one of claims 10 and 11, characterised in that the prepared  
tablets or pellets comprising sodium amoxycillin are coating layered with a separating  
layer before application of the enteric coating layer.
13. The use of sodium amoxycillin in the manufacture of an enteric coated oral dosage  
15 form for use in the treatment of *Helicobacter pylori* infections.
14. A method for the treatment of *Helicobacter pylori* infections in mammals and man by  
administration to a host in need thereof a therapeutically effective dose of an enteric coated  
oral dosage for according to any one of claims 1 to 8.

*In vitro* Dissolution of Amoxycillin  
pH 5.90; phosphate buffer ( $\mu = 0.1$ ); 100 r.p.m.; stationary basket





## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00356

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/28, A61K 9/52, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, EMBASE, MEDLINE, WPI, USPATFULL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9702020 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 January 1997 (23.01.97), page 3, line 7 - page 7, line 26, claims --	1-14
X	WO 9525516 A1 (SMITHKLINE BEECHAM PLC), 28 Sept 1995 (28.09.95), page 3, line 24 - page 4, line 36, example 1, claims --	1-14
A	WO 9400112 A1 (AKTIEBOLAGET ASTRA), 6 January 1994 (06.01.94), page 4, line 20 - line 29, example 1, claims -- -----	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&amp;" document member of the same patent family

Date of the actual completion of the international search

25 June 1998

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00356

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Claim 14 is directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compositions.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

09/06/98

International application No.

PCT/SE 98/00356

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9702020 A1	23/01/97	AU 6517496 A EP 0841903 A	05/02/97 20/05/98
WO 9525516 A1	28/09/95	EP 0751771 A GB 9405856 D JP 9510470 T	08/01/97 00/00/00 21/10/97
WO 9400112 A1	06/01/94	AU 4517893 A SE 9201930 D SI 9300330 A	24/01/94 00/00/00 31/12/93



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p><b>(21) International Application Number:</b> PCT/US98/09449</p> <p><b>(22) International Filing Date:</b> 8 May 1998 (08.05.98)</p> <p><b>(30) Priority Data:</b></p> <table border="0"> <tr> <td>60/046,089</td> <td>9 May 1997 (09.05.97)</td> <td>US</td> </tr> <tr> <td>08/950,432</td> <td>15 October 1997 (15.10.97)</td> <td>US</td> </tr> </table> <p><b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</b></p> <table border="0"> <tr> <td>US</td> <td>60/046,089 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>9 May 1997 (09.05.97)</td> </tr> <tr> <td>US</td> <td>08/950,432 (CIP)</td> </tr> <tr> <td>Filed on</td> <td>15 October 1997 (15.10.97)</td> </tr> </table> <p><b>(71) Applicant (for all designated States except US):</b> SAGE PHARMACEUTICALS, INC. [US/US]; 5408 Interstate Avenue, Shreveport, LA 71109 (US).</p> <p><b>(72) Inventor; and</b>  <b>(75) Inventor/Applicant (for US only):</b> CHEN, Jivn-Ren [US/US]; 7614 Brook Haven Way, Shreveport, LA 71105 (US).</p> <p><b>(74) Agent:</b> CHAN, Albert, Wai-Kit; Cooper &amp; Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).</p>		60/046,089	9 May 1997 (09.05.97)	US	08/950,432	15 October 1997 (15.10.97)	US	US	60/046,089 (CIP)	Filed on	9 May 1997 (09.05.97)	US	08/950,432 (CIP)	Filed on	15 October 1997 (15.10.97)	<p><b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i></p>
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<p><b>(57) Abstract</b></p> <p>The present invention relates to new stable enteric coated pharmaceutical dosage forms for oral use containing Omeprazole or Lansoprazole, to a formulation and a method for the manufacture of such a dosage form, and to a method of gastric acid pump inhibition and providing gastrointestinal cytoprotective benefit by using them.</p>																

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STABLE ORAL PHARMACEUTICAL DOSAGE FORMS

This application is a continuation-in-part application of U.S. Serial No. 08/950,432, filed October 15, 1997, claiming priority of U.S. Provisional Application No. 60/046,089, filed May 9, 1997, the content of which is incorporated by reference into this application.

Background of the Invention

U.S. patent number 4,255,431 describes a compound 2-[2-(3,5-dimethyl -4-methoxy)-pyridyl methyl sulfinyl]-(5-methoxy)-benzimidazole (Omeprazole) or pharmaceutically acceptable salt or non-toxic acid addition salt as a therapeutic compound for mammals including man, suffering from gastric acid secretion disturbances.

Omeprazole, however is only stable in basic pH conditions and degrades rapidly in neutral or acid pH environment. For this reason the omeprazole oral dosage form must be protected, not only from the acidic inert ingredients used to make a dosage form but also from the acidic gastric fluid in order to intactly reach the absorption site in the small intestine.

A study [Drug Dev. Ind. Pharm. 21(8), 965 (1995)] showed the effect of pH on the stability of omeprazole solution. The pH-decomposition rate profile curve indicated that the maximum stability was at pH 11. Below pH 7.8 the decomposition was very fast.

A survey of the stability of Omeprazole products from 13 countries was reported [Drug Dev. Ind. Pharm. 22(12), 1173(1996)]. The results of this independent survey of the stability of omeprazole solid dosage forms (20 mg) show that product available in many countries worldwide exhibits a very wide range of stability characteristics. Only 18% of

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total products tested (34) were considered to demonstrate good physical and chemical stability over the course of the study.

5 U.S. patent number 4,628,098 discloses that:

*Lansoprazole is a substituted benzimidazole 2-[[[3-methyl-4- (2,2,2- trifluroethoxy)-2- pyridyl ] methyl ] sulfinyl ] benzimidazole, a compound and a pharmacologically acceptable salt thereof that inhibits gastric acid*  
10 *secretion.*

Lansoprazole is relatively stable when exposed to light. The compound degrades in aqueous solution, the rate of degradation increasing with decreasing pH.

15 It is well known in the pharmaceutical industry that an enteric coating technology is the most efficient means to protect acid unstable medication from the attack of the gastric fluid and can rapidly release the active drug in  
20 the proximal part of the gastrointestinal canal.

An enteric coated dosage form of omeprazole was reported in 1985 by Pilbrant and Cederberg (Scand. J. Gastroenterology 1985; 20 (supp.108) p. 113 - 120). It was found later that  
25 the stability of this dosage form was not sufficient for a long term commercial purpose.

30 Because of the acidic property of the enteric coating polymer, the omeprazole or lansoprazole will degrade and diminish its therapeutic value by direct or indirect contact with it during or after the coating process, even in the presence of alkaline inert ingredients with the active drug in the core particles.

35 DE - AI number 3046 559 teaches a two layer coating system for a dosage form in which the first coating is a water insoluble layer of microcrystalline cellulose and then

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enteric coating as the second layer to release the active drug in the colon.

5 WO number 85/03436 describes a technique to mix active drug with buffering components (i.e. sodium dihydrogen phosphate) to maintain a constant pH in a core for particular purposes. The core is coated with a layer which controls the diffusions.

10 All of these inventions when applied to omeprazole's or lansoprazole's case will not give either an adequate release of active drug or storage stability of such dosage form.

15 U.S. patent number 4,786,505 teaches an art to make an oral pharmaceutical preparation comprising (1) a core consisting of omeprazole plus an alkaline reacting compound (2) an inert subcoating of core (3) an enteric coating of subcoated core and to use it in the treatment of  
20 gastrointestinal disease.

This technique requires a series of cumbersome and laborious pharmaceutical processes: 1) preparation of the core, which should be suitable for multilayer coating 2)  
25 Coating the core with one or more layers of an inert subcoating containing one or more alkaline substances 3) applying an outer enteric coating to the subcoated core 4) make the pharmaceutical preparation for therapeutical use.

30 U.S. patent number 5,232,706 claims an oral pharmaceutical preparation of omeprazole or an alkali salt of omeprazole and a process for producing such preparation. The design principle of the preparation is basically similar to the U.S. patent number 4,786.505. This preparation is  
35 comprised of: 1) a nucleus of active drug and first basic organic compound; 2) a first coating of nucleus containing at least a layer of a basic water soluble excipient and a



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second basic organic compound; and 3) a second coating formed by an enteric coating.

5 The major difference between U.S. patent number 5,232,706 and U.S. patent number 4,786,505 is the type of basic compound used; the former uses basic organic compound the later uses inorganic alkaline reaction compounds in core and in subcoating.

10 U.S. patent number 5,385,739 relates to a stable formulation of Omeprazole microgranules containing a neutral core of sugar and starch coated with an active layer of drug and mannitol powder mixture with the aid of a solution of a binding agent in water plus ethanol. An  
15 additional protective layer of mannitol and sugar syrup is then applied prior to the final gastroprotection coating.

20 The art of coating a powder mixture containing an active ingredient onto the core of sugar and starch by using a binding solution is a rather difficult process to obtain uniform drug core granules.

25 In addition, two applications of aqueous solution involving the direct contact with Omeprazole, in the coating process, may effect the stability of this moisture-sensitive drug.

30 U.S. patent number 5,399,700 teaches a method for stabilizing an acid unstable benzimidazole derivative, by forming an inclusion complex of Omeprazole with cyclodextrin.

35 This inclusion complex was synthesized in an aqueous alkaline solution at 40° - 70°C and then used to manufacture a tablet which is first coated by a water soluble substance and then with an enteric substance to form an enteric coated oral drug.

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The safety of cyclodextrin for human oral dosage form needs to be clarified. Even if the acid stability and dissolution characterization of this inclusion complex has been well demonstrated in vitro, its behavior in vivo is not referenced in this patent.

U.S. patent number 4,689,333 claims a pharmaceutical composition for preventing or treating digestive ulcers or gastritis which contains an effective amount of Lansoprazole or a pharmacologically acceptable salt thereof and pharmacologically acceptable carriers.

A study [Drug Dev. Ind. pharm. 18 (13), 1437 (1992)] reported that enteric granule formulations for Lansoprazole was established, however, it was difficult because some of the excipients needed for these formulations are incompatible with the drug. The alkaline stabilizers were then screened and the optimal pH stability of 9 was suggested in this paper.

A continued study from the above mentioned effort [Drug Dev. Ind. pharm. 20(9), 1661 (1994)] attempted to prepare more stable enteric granules without using these troublesome excipients by using a centrifugal fluid-bed granulator instead of an extruder-spheronizer. It was said that with this method more stable enteric granules could be obtained. The utilization of special sophisticated equipment to achieve the stable granules may suffer economical disadvantages.

U.S. patent number 5,026,560 discloses spherical granules having a seed core coated with a binder and spraying powder containing lansoprazole as active drug, low substituted hydroxypropylcellulose and magnesium or calcium carbonate as alkaline agents. The powder coated core is further coated with spraying powder of low substituted hydroxypropylcellulose and then with enteric coating agent.

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Technically, powder coating in pharmaceutical manufacturing brings forth issues such as content uniformity of the active on the seed core, laborious process attention and time consumption. It therefore tremendously increases the cost of the product.

U.S. patent number 5,045,321 describes a pharmaceutical composition for coated tablets or granules, which is comprised of lansoprazole being in contact with at least one of the basic inorganic salts evenly. No protective and/or enteric coating is mentioned in the patent claim.

U.S. patent number 5,093,132 is similar to the U.S. patent number 5,045,321 but more specifically, describes an oral stabilized pharmaceutical composition for the inhibition of gastric acid secretion comprising of lansoprazole or its pharmaceutically acceptable salt in contact evenly with a basic inorganic salt stabilizing agent. It also mentions simply an enteric coating for the composition.

Enteric coated oral solid dosage forms have been in existence for a century. U.S. patent number 3,656,997 and 3,959,540 disclosed a coated gastric juice resistant capsules and process for the production thereof. Most commercially available products under this category are coated pellets or granule filled capsules and tablet dosage forms. The concept of an enteric coated capsule dosage for commercial purposes are relatively new. So far, only one prescription product - VIVOTIF BERNA<sup>TM</sup> (Berna Products, Co., Coral Gables, Fl.) is in the U.S.A. market.

The advantage of enteric coated capsules are duplex. In addition to the merit natures of enteric coating polymers, the problem involved and the need for extensive efforts in development and the preparation of enteric pellets or tablets can be avoided.

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Historically, enteric coated hard shell capsules were manufactured with formaldehyde treatments. This technology results in a stability problem with this product. Since the successful introduction of a number of enteric polymeric materials, the technology of this coating becomes more popular and is increasingly used in the pharmaceutical industry. However, the use of organic solvents causes risks of air pollution and inflammability. With the advent and availability of aqueous enteric polymer dispersions, manufacturing of enteric coated dosage forms have acquired a great deal of attention. The modern coating equipment now offers to pharmaceutical manufacturers better conditions for the application of aqueous coatings.

The process of enteric coating for pharmaceutical dosage forms are not significantly different with other coating processes. Generally, the sample is first placed in the coating pan or in the fluid-bed chamber for fluidization, while a coating solution is then spraying through a gun according to the two operations: 1) spraying or wetting and 2) drying, which is repeated consecutively during the process.

Summary of the Invention

It is well known that the stability of omeprazole and lansoprazole may be affected adversely in the presence of water and organic solvent, especially by the former.

The previous art of U.S. patent number 4,786,505 and number 5,232,706 all use conventional aqueous wet technologies to make core pellets or granulations. This invention, by preferably using dry mixing of drugs with alkaline substances as core granulations for either capsule filling or direct tablet compression in its processes, can substantially eliminate the stability risk of the active by excluding the moisture from the core granulation.

The alkaline substances in contact with the enteric coating in the aqueous environment can reduce the acid resistance properties of the latter. The invention of the above mentioned two U.S. patents includes the alkaline substances in the subcoating which is directly in contact with the enteric coating, thus it could be detrimental to the gastric fluid resistance of the enteric coating and result in the inferior therapeutic efficacy of omeprazole or lansoprazole.

For this reason the present invention uses a capsule shell as a separating barrier between the alkaline core of active drug and the enteric coatings. In the case of a tablet, only the pure, non-ionic polymer is used as a protective coating.

Furthermore, the present invention describes an improved oral pharmaceutical dosage form for omeprazole, its salt, lansoprazole or its salts. It is comprised of 1) a core powder or granules of active drug and alkaline inorganic or organic substances is formed by dry mixing; 2) said powder or granulation is filled into a hard gelatin capsule or is

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5 further mixed with other pharmaceutical excipients for direct tablet compression; 3) (for tablet only) a conventional pharmaceutical protective coating is disposed on the tablets; and 4) an outer layer of enteric coating is disposed on the dosage form (capsule or tablet).

10 This improved dosage form is more economically feasible in terms of time process and material savings. It is sufficiently stable for commercial distribution and storage. It also effectively protects the active drug from the attack of the acidic gastric fluid and efficiently delivers the active drug to the small intestine.

15 A process for the manufacturing of an oral dosage form of omeprazole or lansoprazole was also described. The details of granulation, encapsulation, tableting and coating art can be found in "The Theory and Practice of Industrial Pharmacy, 1986, Lea & Febiger, Philadelphia, PA, USA, the content of which is incorporated into this application as  
20 a reference.

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Detailed Description of the Invention

This is an invention of an improved pharmaceutical dosage form for oral administration to human being or animal host which is comprised of: (a) a core granulation formed by dry mixing an acid-unstable drug or its salt and an alkaline substance or pharmaceutical excipient without using an aqueous granulating solution; (b) said dry core granulation can then be quantitatively filled into a proper size empty hard gelatin capsule shell using this shell as a barrier and hence eliminating the process of applying a protective coating layer onto the granulation. In other words, this hard gelatin capsule shell constitutes simultaneously a barrier between said core granulation and the outer enteric coating of said capsule during the processing to complete the capsule dosage form; and (c) an enteric coating can then be applied onto said capsule to prevent the capsule from releasing the acid-unstable drug in a low pH environment (i.e. stomach) and then to deliver the drug in a higher pH environment (i.e. small intestine).

As used herein, core granulation is a mixture of a pharmaceutically acceptable granulated alkaline substance and, or excipient, and a drug active ingredient that can be processed into uniform spherelike or regularly shaped aggregates for the improvement of flowability and compressibility. The manufacturing processes may employ one, or a combination of, four established methods:

- 1) dry mixing;
- 2) direct compression;
- 3) milling; and
- 4) non-aqueous granulation.

These methods are described in "The Theory and Practice of Industrial Pharmacy, 1986, Lea & Febiger, Philadelphia, PA,

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USA, edited by Lachman, L., Lieberman, H.A., and Kanig, J.L.

5 This invention also includes an improved pharmaceutical dosage form for oral administration to human being or animal host which consists of: (a) a core granulation formed by dry mixing an acid-unstable drug or its salt, and an alkaline substance or pharmaceutical excipient, without using an aqueous granulating solution, and which can be  
10 directly compressed into a tablet; (b) said tablet can then be filled into an empty, hard gelatin capsule shell using this shell as a barrier and hence eliminating the process of applying a protective layer onto the tablet. In other words, this hard gelatin capsule shell constitutes  
15 simultaneously a barrier between the said tablet and an outer enteric coating of said capsule during the processing to complete the capsule dosage form; and (c) an enteric coating can then be applied onto said capsule to prevent the capsule from releasing the acid-unstable drug in the  
20 low pH environment (i.e. stomach) and then to deliver the drug in a higher pH environment (i.e. small intestine).

Also included in this invention is an improved pharmaceutical dosage form for oral administration to human  
25 being or animal host which consists of: (a) a core granulation formed by dry mixing an acid-unstable drug or its salt, and an alkaline substance or pharmaceutical excipient, without using an aqueous granulating solution, which can then be directly compressed into a tablet; (b)  
30 said tablet can then be coated with a non-ionic protective coating in an organic solvent as a barrier: (1) to separate the acid-unstable active drug in the tablet from the outer enteric coating and, (2) to protect the outer enteric coating from the permeation of generated alkaline solution  
35 formed by any existed water in the core tablet; and (c) an enteric coating then can be applied onto said tablet to protect it from releasing the acid-unstable drug in a low



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pH environment (i.e. the stomach) and to deliver the active in a higher pH environment (i.e. the small intestine).

5 The protective coating can be applied by a standard film coating procedure in a suitable coating machine using a non-aqueous solution. The non-ionic protective polymer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and polyvinylpyrrolidone. The organic solvent  
10 is selected from the group consisting of isopropyl alcohol, methanol and ethanol. Other appropriate non-ionic protective polymer may be similarly used.

15 The plasticizer for protective coating includes, but is not limited to, triethyl citrate, propylene glycol and polyethylene glycol 6000.

20 In a preferred embodiment, the drug active ingredient comprises Omeprazole, salt of Omeprazole - selected from the group consisting of sodium, potassium, calcium and ammonium salts, Lansoprazole or salt of Lansoprazole.

25 In another embodiment, the alkaline substance of dosage form mentioned above comprises one or any combination of the following: (a) alkaline metallic salt of carbonic acid: calcium carbonate, granulated calcium carbonate; (b) dicalcium phosphate anhydrous, Dibasic sodium phosphate anhydrous, tricalcium phosphate, anhydrous; (c) sodium carboxymethylcellulose, calcium carboxymethylcellulose; (d)  
30 magnesium aluminum silicate; (e) sodium lauryl sulfate; (f) sodium bicarbonate; and (g) microcrystalline cellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose.

35 Also in another embodiment, the pharmaceutical excipient mentioned in the above dosage forms may be selected from one or any combination of the group consisting of dextrose, sorbitol, mannitol, starch, dextrin, maltodextrin, lactose,

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magnesium stearate, calcium stearate, talc, microcrystalline cellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose.

5 Also in another embodiment, the pharmaceutical excipient mentioned in the above dosage forms may be selected from one or any combination of the group consisting of dextrose, sorbitol, mannitol, starch, dextrin, maltodextrin, lactose, magnesium stearate, calcium stearate, talc,  
10 microcrystalline cellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose. Other appropriate excipients may be similarly used.

In a separate embodiment, the enteric coating comprises:  
15 (a) cellulose acetate phthalate, (C-A-P) cellulose acetate trimellitate (C-A-T), Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS), Hydroxypropyl Methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), Anionic phthalate polymers based on methacrylic acid and  
20 methacrylic acid esters; (b) compounds either alone or in any combination in organic solvent, (i.e isopropyl alcohol, methanol, ethanol or ethyl acetate) containing at least one plasticizer (i.e. triethyl citrate, polyethylene glycol 6000 or glycerol monostearate, as a coating solution; (c)  
25 the group of compounds in (a) either alone or in any combination in aqueous dispersion containing at least one plasticizer can be an alternative coating solution; and (d) the process to apply the coating solution or dispersion to said capsules or tablets is a conventional pharmaceutical  
30 method. The coating procedures are performed in a suitable coating machine.

This invention provides a process for manufacturing the capsule dosage form of above described drug which comprises  
35 steps of: (a) preparing the granulation by preferably dry mixing the active ingredient and alkaline substance(s) or by non-aqueous wet granulation method using only the

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pharmaceutically acceptable organic solvent, preferably methanol, ethanol or isopropyl alcohol as wetting solution and drying the granulation; (b) filling the capsule with the dried granulation; and (c) coating the capsules with an enteric coating solution or dispersion solution described above.

This invention provides a aqueous-free process for manufacturing the tablet dosage form that comprises steps of (a) preparing the granulation by preferably dry mixing the active ingredient and alkaline substance or pharmaceutical excipients; (b) directly compressing the granulation into a tablet by a conventional method; (c) filling the tablet into an empty hard gelatin capsule shell and; (d) coating the capsule with an enteric coating.

This invention provides an improved pharmaceutical dosage form for oral administration to human being or animal host containing an acid-unstable drug active ingredient which comprises: (a) a core tablet formed by dry mixing drug or its salt with alkaline substance and pharmaceutical excipient or excipients and directly compressing, which can be coated with a protective layer as a barrier to: (i) separate the acid-unstable active drug in the core from the outer enteric coating; and (ii) protect the entered coating from the permeation of alkaline solution formed by water in the core tablet; and (b) an enteric coating disposed on said protectively coated tablet to protect it from releasing the acid-unstable drug in the stomach and to deliver the active to the small intestine. In an embodiment of the above process for manufacturing the improved pharmaceutical dosage form, the core granulation is prepared by dry mixing, direct tablet compressing, subcoating the tablet with organic solvent base protective coating; and coating the subcoated tablets with an enteric coating solution or dispersion.

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This invention provides an improved pharmaceutical dosage form for oral administration to human being or animal host containing an acid-unstable drug active ingredient which comprises: (a) a core tablet formed by dry mixing drug or its salt with alkaline substance and pharmaceutical excipient or excipients and directly compressing, which can then be coated with a protective layer as a barrier to: (i) separate the acid-unstable active drug in the core from the outer enteric coating; and (ii) protect the enteric coating from the permeation of alkaline solution formed by water in the core tablet; (b) an enteric coating disposed on said protectively coated tablet to prevent it from releasing the acid-unstable drug in the stomach and to deliver the active to the small intestine; and (c) this tablet is then filled into an empty hard gelatine capsule shell to form a final dosage form. In an embodiment of the above process for manufacturing the improved pharmaceutical dosage form, the core granulation is prepared by dry mixing, direct tablet compressing, subcoating the tablet with organic solvent base protective coating, coating the subcoated tablets with an enteric coating solution or dispersion and filling the said enteric coated tablet into an empty hard gelatin capsule.

#### Example 1.

##### Core Granulations: Non-Aqueous Wet Granulation:

A. Ten grams of Omeprazole were granulated with 10 ml. of ethyl alcohol with agitation. The moist granules were dried and screened to obtain a uniform granule size.

B. A suspension of Omeprazole being 10 grams in 50 ml. of ethyl alcohol was added into 100 grams of an alkaline inert compound being calcium carbonate granules (DELAVAL, Philadelphia, PA) with agitation to mix homogeneously the liquid and solids. The moist

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granules were dried and screened for uniform and adequate granule size.

- 5 C. Same as Example 1.B., except the alkaline substance is calcium carbonate 90A (Particle Dynamics, Inc., St. Louis, MO.)
- 10 D. A mixture of 16 grams of Omeprazole and 10 grams of povidone USP was dispersed in 15 ml. of ethyl alcohol. The rest of the procedure is same as Example 1.B. above except that the dispersion was used to replace the suspension for 84 grams of alkaline substance.
- 15 E. Ten grams of sodium carboxymethylcellulose was dispersed in 10 ml. of ethyl alcohol. This liquid was then used to granulate a mixture of 2 grams of Omeprazole and 5 grams of calcium carbonate 90A (same as that used in Example 1.C.). The remaining portion of the procedure is the same as Example 1.B. above.
- 20

### Example 2.

#### Core Granulation: Dry Mixing:

- 25 A. Ten grams of Omeprazole were mixed with an alkaline substance being tricalcium phosphate anhydrous USP/NF and then passed through a screen to obtain a homogenous granule size.
- 30 B. Same as Example 2.A. above except the alkaline substance is pharmaceutical excipient microcrystalline cellulose USP/NF.
- 35 C. Same as Example 2.A. above except the alkaline substance is pharmaceutical excipient lactose, anhydrous USP.

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D. Same as Example 2.A. above except the alkaline substance is pharmaceutical excipient maltodextrin.

5 E. Same as Example 2.A. above except the alkaline substance is Calcium Carbonate 90A (same as Example 1.C. above).

10 F. Same as Example 2.A. above except the alkaline substance is Calcium Carbonate granules (same as Example 1.B. above).

15 G. Same as Example 2.A. above except the alkaline substance is Sodium carboxymethylcellulose.

### Example 3.

#### Encapsulation:

20 The individual core granulation was mixed with 2% to 5% talc used as a lubricant, and then quantitatively encapsulated in hard gelatin capsules by known pharmaceutical techniques.

### Example 4.

#### Direct Tablet Compression:

30 A. The individual core granulation was mixed with Lactose and Talc or magnesium stearate, and compressed into tablets by known pharmaceutical techniques.

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**Example 5.**Capsule Enteric Coating:

5 The hard gelatine capsules obtained from Example 3. above were enteric coated in a conventional film coating machine with the following coating solutions by known pharmaceutical techniques.

10 Eudragit L-100 <sup>®</sup> (Methacrylic Acid Copolymer) 600 Grams  
Isopropyl Alcohol 8,600 Grams  
Triethyl Citrate 60 Grams  
FD&C or D&C aluminum laks 300 Grams  
Purified water 400 Grams

15

**Example 6.****A. Tablet Protective Coating:**

20

The tablets obtained from Example 4. were coated in a conventional film coating machine with the following coating solution by known pharmaceutical techniques.

25 Methocel E15 <sup>®</sup> (Hydroxypropylmethylcellulose) 500 Grams  
Polyethylene Glycol E400 110 Grams  
Ethyl Alcohol 10,000 Grams

**B. Enteric Coating for Tablets:**

30

The coated tablets obtained from Example 6.A. were enteric coated in a conventional film coating machine with the coating solution being the same as that used in Example 5. by a known pharmaceutical technique.

35

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**Example 7.**Coated Tablet in a Capsule:

5       The coated tablets obtained from Example 6.B. were encapsulated in empty hard gelatin capsules to form a capsule product.

10

**Example 8.**

Several formulations were placed in ambient room temperature conditions for stability studies. The color changes of the core granulations were observed. Some of  
15       the formulations are assayed using USP High Pressure Liquid Chromatographic (HPLC) methods to determine the amount of drug remaining. The results are shown on Table 1. below.



-20-

Table 1.

Example	Stabliity Time Period	Color	% o f
Omeprazole			
Number	(Months)	Change	Remaining
1.A.	26	+	N/A
1.B.	26	0 to +	99.8
1.C.	26	0 to +	65.1
1.D.	26	0 to +	96.3
1.E.	11	+++	N/A
2.A.	13	0	89.6
2.B.	13	0	N/A
2.C.	11	+	91.0
2.D.	11	++	88.2
2.E. +3	11	0 to +	33.6
2.F. +3	11	0 to +	97.8
2.G.	11	0	96.2
2.C. +4	11	0 to +	N/A
2.F. +3+5	11	0 to +	96.4
2.F. +6+7	11	0 to +	95.5

0 = no change

+ = intensity of color change

N/A no assay was performed

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What is claimed is:

1. An improved pharmaceutical dosage form for oral  
administration to human being or animal host  
5 containing an acid-unstable drug active ingredient  
which comprises:
  - (a) a core granulation formed by dry mixing drug or  
its salt with alkaline substance and  
pharmaceutical excipient or excipients which can  
10 be quantitatively filled into an empty hard  
gelatin capsule shell;
  - (b) this hard gelatine capsule shell which  
constitutes simultaneously a separated barrier  
between the said core granulation and further  
15 processed outer enteric coating of said capsule  
during the completion of dosage form; and
  - (c) an enteric coating disposed on said capsule to  
prevent the capsule dosage form from releasing  
the acid-unstable drug or its salt in the gastric  
20 environment and to deliver it in the intestinal  
environment.
2. An improved pharmaceutical dosage form for oral  
administration to human being or animal host  
25 containing an acid-unstable drug active ingredient  
which comprises:
  - (a) a core tablet formed by dry mixing drug or its  
salt with alkaline substance, pharmaceutical  
excipient or excipients and directly compressing,  
30 which can be filled into an empty hard gelatin  
capsule shell;
  - (b) this hard gelatin capsule shell which constitutes  
simultaneously a separated barrier between the  
said core tablet and further processed outer  
35 enteric coating of said capsule during the  
completion of dosage form; and
  - (c) an enteric coating disposed on said capsule to

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protect the capsule dosage form from releasing the acid-unstable drug or its salt in the gastric environment and to deliver it in the intestinal environment.

5

3. An improved pharmaceutical dosage form for oral administration to human being or animal host containing an acid-unstable drug active ingredient which comprises:

10

- (a) a core tablet formed by dry mixing drug or its salt with alkaline substance and pharmaceutical excipient or excipients and directly compressing, which can be coated with a protective layer as a barrier to:

15

- (i) separate the acid-unstable active drug in the core from the outer enteric coating; and

- (ii) protect the entered coating from the permeation of alkaline solution formed by water in the core tablet; and

20

- (b) an enteric coating disposed on said protectively coated tablet to protect it from releasing the acid-unstable drug in the stomach and to deliver the active to the small intestine.

25

4. An improved pharmaceutical dosage form for oral administration to human being or animal host containing an acid-unstable drug active ingredient which comprises:

30

- (a) a core tablet formed by dry mixing drug or its salt with alkaline substance and pharmaceutical excipient or excipients and directly compressing, which can then be coated with a protective layer as a barrier to:

35

- (i) separate the acid-unstable active drug in the core from the outer enteric coating; and

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- (ii) protect the enteric coating from the permeation of alkaline solution formed by water in the core tablet;
- (b) an enteric coating disposed on said protectively coated tablet to prevent it from releasing the acid-unstable drug in the stomach and to deliver the active to the small intestine; and
- (c) this tablet is then filled into an empty hard gelatine capsule shell to form a final dosage form.
- 5.
- The dosage form according to claim 1 or 2 or 3 or 4 wherein the drug active ingredient is selected from the group consisting of omeprazole, sodium omeprazole, potassium omeprazole, calcium omeprazole, ammonium omeprazole, lansoprazole and pharmaceutical salt of lansoprazole.
- 6.
- The dosage form according to claim 1 or 2 or 3 or 4 wherein the alkaline substance is selected from one or any combination of the group consisting of alkaline metallic salt of carbonic acid, calcium carbonate, granulated calcium carbonate, dicalcium phosphate anhydrous, dibasic sodium phosphate anhydrous, tricalcium phosphate anhydrous, sodium carboxymethylcellulose, calcium carbosymethylcellulose, magnesium aluminum silicate, sodium lauryl sulfate and sodium bicarbonate.
- 7.
- The dosage form according to claim 2 or 3 or 4 wherein the pharmaceutical excipient is selected from one, or any combination of the group consisting of dextrose, sorbitol, mannitol, starch, dextrin, maltodextrin, lactose, magnesium stearate, calcium stearate, talc, microcrystalline cellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose.

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8. A dosage form according to claim 1 or 2 or 3 or 4 wherein the enteric coating comprises:

(a) enteric polymer selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, anionic polymers based on methacrylic acid and methacrylic acid esters;

(b) organic solvent selected from the group consisting of isopropyl alcohol, methanol, ethanol and ethyl acetate; to make polymer solution and aqueous system to make aqueous dispersion of polymer; and

(c) plasticizer selected from the group consisting of triethyl citrate, polyethylene glycol 6000 and glycerol monostearate.

9. The dosage form according to claim 3 or 4 wherein the protective coating comprises:

(a) non-ionic protective polymer selected from the group consisting of hydroxypropyl methylcellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose polyvinylpyrrolidone.

(b) organic solvent selected from the group consisting of isopropyl alcohol, methanol and ethanol; and

(c) plasticizer selected from the group consisting of triethyl citrate, propylene glycol and polyethylene glycol 6000.

10. A process for manufacturing the improved pharmaceutical dosage form of claim 1 comprises:

(a) preparing the core granulation by dry mixing the drug active ingredient with alkaline substance or by granulating with organic solvent the said mixture and drying;

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- (b) filling the said dried core granulation into an empty hard gelatin capsule shell; and
- (c) coating the said capsule with an enteric coating solution or dispersion.

5

11. A process for manufacturing the improved pharmaceutical dosage form of claim 2 comprises:

10

- (a) preparing the core granulation by dry mixing the drug active ingredient with alkaline substance and pharmaceutical excipients;
- (b) directly compressing the said core granulation into tablets;
- (c) filling the said tablet into an empty hard gelatin capsule shell; and
- (d) coating the said capsule with an enteric coating solution or dispersion.

15

12. A process for manufacturing the improved pharmaceutical dosage form of claim 3 comprises preparing the core granulation by dry mixing, direct tablet compressing, subcoating the tablet with organic solvent base protective coating; and coating the subcoated tablets with an enteric coating solution or dispersion.

20

13. A process for manufacturing the improved pharmaceutical dosage form of claim 4 comprises preparing the core granulation by dry mixing, direct tablet compressing, subcoating the tablet with organic solvent base protective coating, coating the subcoated tablets with an enteric coating solution or dispersion, and filling the said enteric coated tablet into an empty hard gelatine capsule.

25

30

35

## INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/40, 9/14, 9/48, 9/52, 9/62

US CL : 424/463

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/463, 478, 474, 484, 488

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/01783 A1 (ASTRA AKTIEBOLAG) 19 JANUARY 1995 See entire document.	1-13
A	US 4,910,021 A (DAVIS ET AL) 20 MARCH 1990, see entire document.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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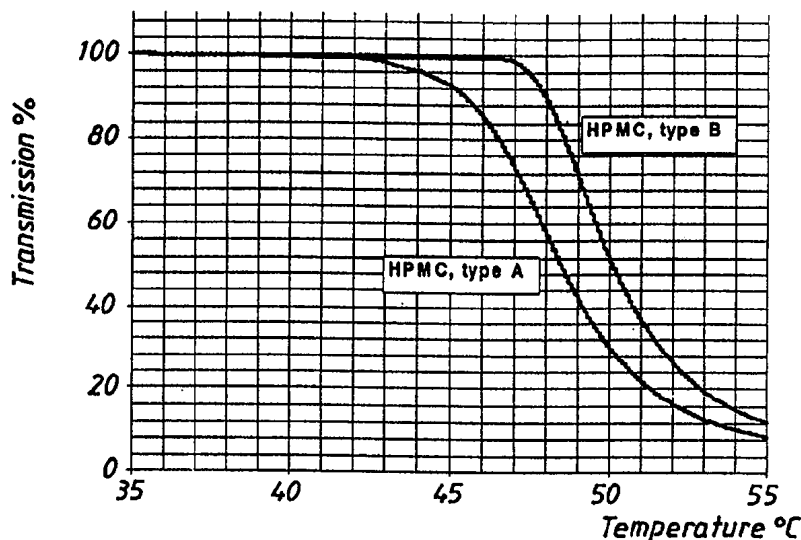


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(54) Title: PHARMACEUTICAL FORMULATION OF OMEPRAZOLE



(57) Abstract

An enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with a pharmaceutically acceptable excipient, such as for instance a binding agent, and on said core material a separating layer and an enteric coating layer. A hydroxypropyl methylcellulose (HPMC) of low viscosity with a specific cloud point is used in the manufacture of pharmaceutical formulations. Furthermore, the application describes the processes for their preparation and the use of the claimed formulations in medicine.



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## PHARMACEUTICAL FORMULATION OF OMEPRAZOLE

Field of the invention.

5 The present invention relates to an oral pharmaceutical formulation comprising the acid labile  $H^+$ ,  $K^+$ -ATPase inhibitor omeprazole. The formulation is in the form of a multiple unit dosage form comprising enteric coating layered units of omeprazole. More specifically, the units comprise a core material of omeprazole and optionally an alkaline reacting substance, in admixture with one or more pharmaceutically acceptable excipients  
10 such as a binding, filling and/or disintegrating agent. Furthermore, each unit comprises a separating layer to separate the enteric coating layer from the core material. The separating layer and/or the optional binding agent consists of a specific quality of hydroxypropyl methylcellulose (HPMC), and optionally pharmaceutical excipients. More specifically, the HPMC quality has a specific cloud point.

15 Furthermore, the present invention refers to the use of a specific quality of HPMC in the manufacture of a pharmaceutical formulation comprising omeprazole, and the use of such a pharmaceutical formulation in medicine.

Background of the invention.

20 Omeprazole, an alkaline salt thereof, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, all compounds hereinafter referred to as omeprazole, are used in the treatment of gastric acid related diseases. Omeprazole and pharmaceutically acceptable salts thereof are described in EP 5129, and some specific alkaline salts of  
25 omeprazole are described in EP 124 495 and WO95/01977. Certain salts of the single enantiomers of omeprazole and their preparation are described in WO94/27988.

Omeprazole is generally known to be useful for inhibiting gastric acid secretion in mammals and man by controlling gastric acid secretion at the final step of the acid  
30 secretory pathway. Thus, in a more general sense, it may be used for prevention and

treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with non ulcer dyspepsia, in  
5 patients with symptomatic gastro-oesophageal reflux disease, and in patients with gastrinomas. It may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases  
10 related to these, as well as in the treatment or prophylaxis of inflammatory conditions in mammals, including man.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The degradation is catalyzed by acidic compounds and is stabilized in mixtures with  
15 alkaline compounds. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light.

With respect to the stability properties of omeprazole, it is obvious that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must  
20 be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical oral dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. In EP 247 983 such an enteric coated  
25 formulation of omeprazole is described. The formulation contains omeprazole in the form of a core unit containing omeprazole together with an alkaline salt or containing an alkaline salt of omeprazole optionally together with an alkaline salt, the core unit is layered with a separating layer and an enteric coating layer. In WO 96/01623 a multiple unit tableted dosage formulation of omeprazole is described.

The oral formulations described in EP 247 983 and the tablet formulations described in WO 96/01623 are enteric coating layered formulations which comprise or may comprise a separating layer to separate the acidic enteric coating material from omeprazole being an acid susceptible substance. HPMC of low viscosity may be used as a binding agent in the core material or as a layer separating the core material from the enteric coating layer in the described formulations. All ingredients, including HPMC qualities, used in a pharmaceutical preparations must fulfill strict criteria, such as for instance requirements defined in pharmacopoeial monographs.

The rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole into the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). Therefore the limits for rate of release of the omeprazole from the pharmaceutical formulation are stated in the marketing approval for the products.

It has now surprisingly been found that different batches of low viscosity HPMC, which fulfill all pharmacopoeial requirements, used as binder in the formation of omeprazole containing cores or as material for the separating layer of enteric coating layered formulations of omeprazole, may differ with respect to their ability of influencing the rate of release of omeprazole in simulated intestinal fluid, USP, *in vitro*. One parameter of interest in the release rate influencing ability of the HPMC is its water solubility.

The aqueous solubility of HPMC decreases with increasing temperature due to polymer phase separation. This is observed as a clouding of the polymer solution when the temperature is increased. Cloud point is the temperature at which this polymer phase separation occurs. Cloud point is determined by measuring the light transmission through the polymer solution. The light transmission of a specific system where the polymer is dissolved, that is a transparent polymer solution without clouding, is defined as light transmission 100 %. In this patent application cloud point is defined as the temperature where the light transmission of a specific system is 96% when a commercial instrument

from Mettler is used. For other cloud point systems and instruments another light transmission may be specified for each system.

One problem which can be avoided by the new formulation and use of a specific quality of HPMC is that the amount of product discard can be reduced. From an economical aspect it is advantageous to specify and check the HPMC quality and keep the discard of produced pharmaceutical product low.

#### Outline of the invention.

It has now been found that a quality of HPMC with a cloud point of not less than 45.6°C determined as the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP 81C instrument is desirable in an enteric coating layered pharmaceutical formulation comprising omeprazole. Alternatively, when another instrument is used for determination, the cloud point may be specified as not less than 44.5°C when determined as the temperature where the light transmission is 95% measured by a spectrophotometer. The two different apparatuses used in cloud point determination are described more in detail in the experimental section, below. An upper limit for the cloud point is not critical and therefore there is no need to specify that.

The HPMC is used as a binding agent and/or as a constituent of a separating layer separating the core material from the enteric coating layer. The HPMC quality defined in the present patent application is desirable in fulfilling the criteria on rate of release of omeprazole and to be suitable for oral administration of omeprazole.

#### Detailed description of the drawings.

Figure 1 shows two graphs representing two different batches of low viscosity HPMC named Type A and Type B. The graphs show cloud point determinations for the two HPMC batches used as a constituent of the separating layer described in Example 1 below. With a separating layer comprising HPMC Type A the release of omeprazole was not

acceptable for a pharmaceutical product, and with the HPMC Type B none of the discussed problems with the rate of release of omeprazole in an oral formulation occurred.

Figure 2 shows the same experiment as Figure 1 described in Example 2 below, but the cloud point determination has been performed in another equipment.

5

Figure 3 shows two graphs representing the release of omeprazole from core material with two different batches of low viscosity HPMC used as binding agent described in Example 3 below. The bars represent standard error of the mean. The release of omeprazole was followed by spectrophotometric determinations at 302 nm, and the graphs show that the release of omeprazole was delayed with a binding agent of the HPMC Type A compared with Type B.

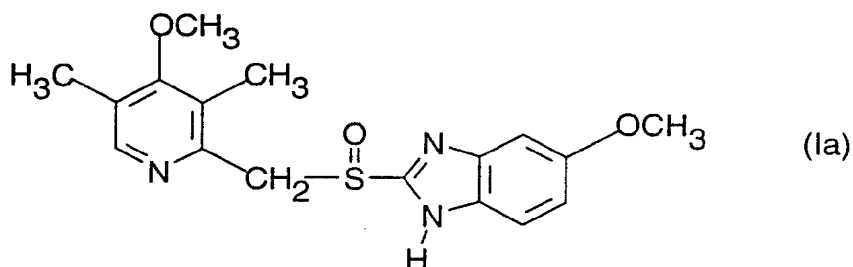
10

#### Detailed description of the invention.

##### 15 Core materials.

Omeprazole with formula Ia, is preferably formulated into an oral composition in the form of a pharmaceutically acceptable salt, such as an alkaline salt selected from the group of the  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Na^{+}$  and  $K^{+}$  salts, more preferably the  $Mg^{2+}$  salt. Omeprazole may also be used in the form of the (-)-enantiomer of omeprazole or an alkaline salt of the (-)-enantiomer of omeprazole.

20



25 The core material for the individually enteric coating layered pellets can be composed and formulated according to different principles, such as described in EP 247 983 and WO

96/01623 hereby incorporated by reference. For instance, omeprazole is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of omeprazole in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives, can be used.

Preferably, omeprazole, optionally after mixing with alkaline compounds, is mixed with suitable constituents including a binding agent and formulated into a core material. Said core materials may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. The formulated core materials may have a size of less than approximately 2 mm. The manufactured core materials can be layered further with additional ingredients, optionally comprising active substance, and/or be used for further processing.

Alternatively, inert seeds layered with active substance (the active substance is optionally mixed with alkaline compounds) can be used as the core material for the further processing. The seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures.

Before the seeds are layered, for instance by using granulating or spray coating/layering equipment, omeprazole is mixed with a binding agent and optionally further components. Such further components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

The binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, microcrystalline cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. If hydroxypropyl methylcellulose is used as the binding agent, it is preferably a quality of HPMC with a cloud point of not less than 45.6°C determined as

the temperature where the light transmission of a specified system is 96% measured by a Mettler FP90/FP81C instrument, or alternatively the HPMC quality has a cloud point of not less than 44.5°C determined as the temperature where the light transmission is 95% measured by a spectrophotometer. Suitable surfactants are found in the groups of  
5 pharmaceutically acceptable non-ionic or ionic surfactants, such as for instance sodium lauryl sulphate.

The active substance may also be mixed with an alkaline pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to,  
10 substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  
15  $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$  or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or  
20 spray congealing technique.

#### Separating layer(s)

The core material containing omeprazole must, according to EP 247 983, be separated from the enteric coating polymer(s) containing free carboxyl groups, which may otherwise cause  
25 degradation/dicolouration of omeprazole during the coating process or during storage.

According to the present invention, the separating layer comprises a specific quality of low viscosity HPMC, especially a HPMC with a viscosity of preferably less than 7.2 cps in 2% aqueous solution. This specific quality of HPMC should preferably have a cloud point of  
30 at least 45.6 °C determined by a Mettler instrument. The determination of cloud point may



be performed in another instrument and system as described in detail in the experimental section. The cloud point is determined in a mixed disodium hydrogenphosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5. The mixed solution used for the cloud point determination has a pH of 6.75 - 6.85. The concentration of HPMC in the mixed solution is 1.2% (w/w) for the Mettler instrument. For more detailed information on the composition of the mixed solution, see below in the experimental section.

Alternatively, the quality of HPMC is determined by a method which correlates with the above described methods, e.g. NIR spectrophotometry.

Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the separating layer(s).

#### Enteric coating layer(s)

One or more enteric coating layers are applied onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in a suitable organic solvent. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s). For environmental reasons, an aqueous coating process may be preferred.

In such aqueous processes methacrylic acid copolymers are most preferred.

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain desirable mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for each enteric coating layer

formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s). Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included in the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acidic susceptible active substance.

To protect the acidic susceptible active substance, the enteric coating layer(s) preferably constitute(s) a thickness of at least approximately 10  $\mu\text{m}$ . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

The pellets or units covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the layering process.

#### Final dosage form.

The prepared pellets may be filled in hard gelatine capsules or compressed with suitable tablet excipients into a tableted multiple unit formulation. Final dosage forms include effervescent tablets, and also combinations of omeprazole with other active ingredients, such as for instance antibacterial substances, NSAID(s), motility agents or antacids.

#### Experimental section.

Examples 1 and 2: Test of omeprazole pellets layered with two different types of low viscosity HPMC used as a constituent of the separation layer.

Omeprazole pellets prepared according to the description in EP 247 983 (correspond to pellets from a Losec<sup>®</sup> capsule) were tested with respect to rate of release of omeprazole.

According to the marketing approval for the Losec<sup>®</sup> capsule formulation at least 75 % of the omeprazole in a dose must be released within 30 minutes in a buffer solution.

The pellets were pre-exposed to simulated gastric fluid USP (without enzyme) at 37°C for 2 hours. Thereafter the drug release in buffer solution pH 6.8 at 30 minutes was determined by liquid chromatography. The buffer solution pH 6.8 was a mixture of 100.0 parts of simulated gastric fluid USP (without enzyme) and 80.0 parts of 0.235 M disodium hydrogen phosphate solution, pH should be between 6.75 and 6.85. The simulated gastric fluid USP (without enzyme) was prepared by dissolving 2.0 g NaCl and 7.0 ml conc. HCl and add water to 1000 ml. The 0.235 M disodium hydrogen phosphate solution was prepared by dissolving 41.8 g Na<sub>2</sub>HPO<sub>4</sub>·2H<sub>2</sub>O and add water to 1000 ml.

The composition of the tested omeprazole pellets was as follows.

I. Core material with the following composition was prepared.

Core material

Omeprazole	10.4	kg
Mannitol	74.3	kg
Hydroxypropylcellulose	3.1	kg
Microcrystalline cellulose	2.1	kg
Lactose anhydrous	4.2	kg
Disodium hydrogen phosphate	0.41	kg
Sodium lauryl sulphate	0.26	kg
Water approx	19	kg

II. The prepared core material was coating layered with a separating layer consisting of HPMC, type A or type B. The separating layers with the following composition were applied in the stated amount.

Separating layer

Uncoated pellets from above	120	kg
Hydroxypropyl methylcellulose 6cps	4.8	kg
Water	96	kg

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III. The prepared core material with a separating layer was further coating layered with an enteric coating of the following composition.

Enteric coating layer

10	Prepared pellets from above	120	kg
	Methacrylic acid copolymer	27.3	kg
	Polyethylene glycol	2.7	kg
	Water	150	kg

15 Omeprazole pellets prepared with separating layer of two different qualities of HPMC 6cps, i.e type A and type B, were tested according to the description above. The pellets were prepared from the same batch of omeprazole, and with the same enteric coating material. The release of omeprazole within 30 minutes in a buffer solution was determined.

20 Cloud point determination was performed with two different apparatuses. In Example 1 a commercial equipment from Mettlers was used and in Example 2 a spectrophotometer equipped with a heating coil and stirring function was used. The experimental conditions and used apparatuses are described below.

Pellets containing HPMC	Cloud point [°C]		Release of omeprazole from enteric coated pellets [%]
	Ex. 1 (n=2)	Ex. 2 (n=1)	
Type A	44.4	42.5	69 (60-84)
Type B	47.5	47.2	93 (93-94)

The results from cloud point determination for the two HPMC qualities are shown in Figures 1 and 2. As can be seen in the table above with the HPMC Type A the release of omeprazole was not acceptable for a pharmaceutical product, but with the HPMC Type B none of the discussed problems with the rate of release of omeprazole in an oral  
5 formulation occurred.

Results from a number of experiments with different batches of HPMC indicate that HPMC with a cloud point of at least 45.6°C is desirable in fulfilling the regulatory requirements on rate of release of omeprazole, when the cloud point determination is  
10 performed in a commercial Mettler instrument.

Cloud point determination of the HPMC types in the Mettler instrument was conducted in the following way. The cloud point of the HPMC types was determined in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5. The  
15 mixed solution had a pH of 6.75 - 6.85. The concentration of HPMC 6 cps in the mixed solution was 1.2% (w/w). It is essential for the specificity of the cloud point determination that this system is used in the chosen instrument. The Mettler instrument comprises the following parts: Mettler FP90 Central processor, FP81C Measuring unit and ME-18572 boiling point tubes. A temperature range of 35.0 to 55.0°C was used and a heating rate of  
20 1.0°C/min. The results are shown in Figure 1.

Alternatively, a spectrophotometer equipped with a heating coil and a stirring function was used for the cloud point determination. The concentration of HPMC in the buffer solution was 1.0% (w/w). The equipment measured corresponding temperature and transmission  
25 values. Depending on the character of the HPMC to be analysed, the temperature interval of interest varies. A temperature range of 35 - 50°C was relevant for most samples. A delay time of 5 minutes at each new temperature setting was used before transmission reading. The results are shown in Figure 2.

Example 3: Test of different types of low viscosity HPMC used as binding agent in the preparation of core material for pellets.

- I. Core material with the following composition was prepared by spray layering in a fluidized bed. An aqueous suspension of omeprazole magnesium salt and HPMC was sprayed onto sugar spheres. Two batches of pellets were prepared using HPMC type A and type B, respectively. The same batch of omeprazole-Mg was used for both experiments.

	Sugar spheres	200	g
10	Omeprazole-Mg	200	g
	Hydroxypropyl methylcellulose 6 cps	30	g
	Water	920	g

The prepared pellets were tested with respect to rate of release of omeprazole in buffer solution pH 6.8 with identical composition as in Example 1, 37 °C, paddle speed 100 rpm. The release of omeprazole was followed by spectrophotometric determination (302 nm) and the results are presented in Figure 3. The graphs show that the release of omeprazole was delayed for the HPMC Type A compared with Type B. Since the pellets were not coated with a separating layer and an enteric coating layer they were not pre-exposed to simulated gastric fluid.

Claims.

1. An enteric coated oral pharmaceutical formulation comprising as active ingredient a  
5 compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-  
enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole,  
wherein the formulation comprises a core material of the active ingredient and optionally  
an alkaline reacting compound, the active ingredient is in admixture with one or more  
pharmaceutical acceptable excipients such as a binding, filling and/or a disintegrating  
10 agent, and on said core material a separating layer and an enteric coating layer,  
characterized in that a hydroxypropyl methylcellulose (HPMC) of low viscosity with a  
cloud point of at least 45.6°C determined as the temperature where the light transmission  
of the system is 96%, is used as a binding agent and/or a constituent of the separating layer,  
and wherein the cloud point is determined in the following way: the HPMC is dissolved in  
15 a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and  
simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75-6.85, or that the  
HPMC used as a binding agent and/or a constituent of the separating layer has a low  
viscosity with a cloud point of at least 44.5°C determined as the temperature where the  
light transmission of a system is 95%, and wherein the cloud point is determined in the  
20 following way: the HPMC of low viscosity is dissolved in a concentration of 1% (w/w) in a  
mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the  
proportions 4:5 at a pH of 6.75 - 6.85.
2. A formulation according to claim 1, wherein the HPMC of low viscosity is used as a  
25 constituent of a separating layer.
3. A formulation according to claim 2, wherein the enteric coating layer comprises a  
methacrylic acid copolymer.

4. A formulation according to claim 1, wherein the HPMC of low viscosity is used as a binding agent.
5. A formulation according to claim 1, wherein the HPMC of low viscosity has a  
5 viscosity of less than 7.2 cps in 2% aqueous solution.
6. A formulation according to claim 1, wherein the active ingredient is omeprazole.
7. A formulation according to claim 1, wherein the active ingredient is a magnesium salt  
10 of omeprazole.
8. A formulation according to claim 1, wherein the active ingredient is a magnesium salt of the (-)-enantiomer of omeprazole.
- 15 9. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of  
20 omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with one or more pharmaceutically acceptable excipients such as a binding, filling and/or disintegrating agent and on said core material a separating layer and an enteric coating layer, characterized in that the separating layer comprises a HPMC of low viscosity with a cloud  
25 point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.
10. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a  
30 cloud point of at least 44.5°C at which the light transmission of a system is 95%, in the



manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, the active ingredient is in admixture with one or more pharmaceutically acceptable excipients such as a binding, filling and/or disintegrating agent and on said core material a separating layer and an enteric coating layer, characterized in that the separating layer comprises a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

11. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, in admixture with at least a binding agent, and on said core material at least an enteric coating layer, characterized in that the binding agent is a HPMC of low viscosity with a cloud point as defined above and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

25

12. Use of a quality of hydroxypropyl methylcellulose (HPMC) of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, in the manufacture of an enteric coated oral pharmaceutical formulation comprising as active ingredient a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of

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omeprazole, wherein the formulation comprises a core material of the active ingredient and optionally an alkaline reacting compound, in admixture with at least a binding agent, and on said core material at least an enteric coating layer, characterized in that the binding agent is a HPMC of low viscosity with a cloud point as defined above and the cloud point  
5 is determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

13. Use according to any of claim 9-11 or 12, wherein the HPMC has a viscosity of less  
10 than 7.2 cps in 2% aqueous solution.

14. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound and/or a binding agent, is formulated into a core material and on said core  
15 material a separating layer is coating layered, and thereafter an enteric coating layer is applied, characterized in that the separating layer comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, and the cloud point is determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of  
20 phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

15. A process for the manufacture of an enteric coated oral pharmaceutical formulation defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting  
25 compound and/or a binding agent, is formulated into a core material and on said core material a separating layer is coating layered, and thereafter an enteric coating layer is applied, characterized in that the separating layer comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, and the cloud point is determined in the following  
30 way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of

phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

16. A process for the manufacture of an enteric coated oral pharmaceutical formulation  
5 defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound, is mixed with a binding agent and formulated into a core material, on said core material at least one enteric coating layer is applied, characterized in that the binding agent comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 45.6°C at which the light transmission of a system is 96%, and the cloud point is  
10 determined in the following way: the HPMC is dissolved in a concentration of 1.2% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

17. A process for the manufacture of an enteric coated oral pharmaceutical formulation  
15 defined in claim 1, wherein the active substance optionally mixed with an alkaline reacting compound, is mixed with a binding agent and formulated into a core material, on said core material at least one enteric coating layer is applied, characterized in that the binding agent comprises a hydroxypropyl methylcellulose HPMC of low viscosity with a cloud point of at least 44.5°C at which the light transmission of a system is 95%, and the cloud point is  
20 determined in the following way: the HPMC is dissolved in a concentration of 1% (w/w) in a mixed solution of phosphate buffer 0.235 M and simulated gastric fluid pH 1.2 in the proportions 4:5 at a pH of 6.75 - 6.85.

18. Use of a pharmaceutical formulation as defined in any of claims 1 - 8 for the  
25 manufacture of a medicament for in the treatment of gastrointestinal diseases.

19. A method for the treatment of gastrointestinal diseases in mammals including man by administering to a host in need thereof a therapeutically effective dosage form defined in any of claims 1 - 8.

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Fig. 1

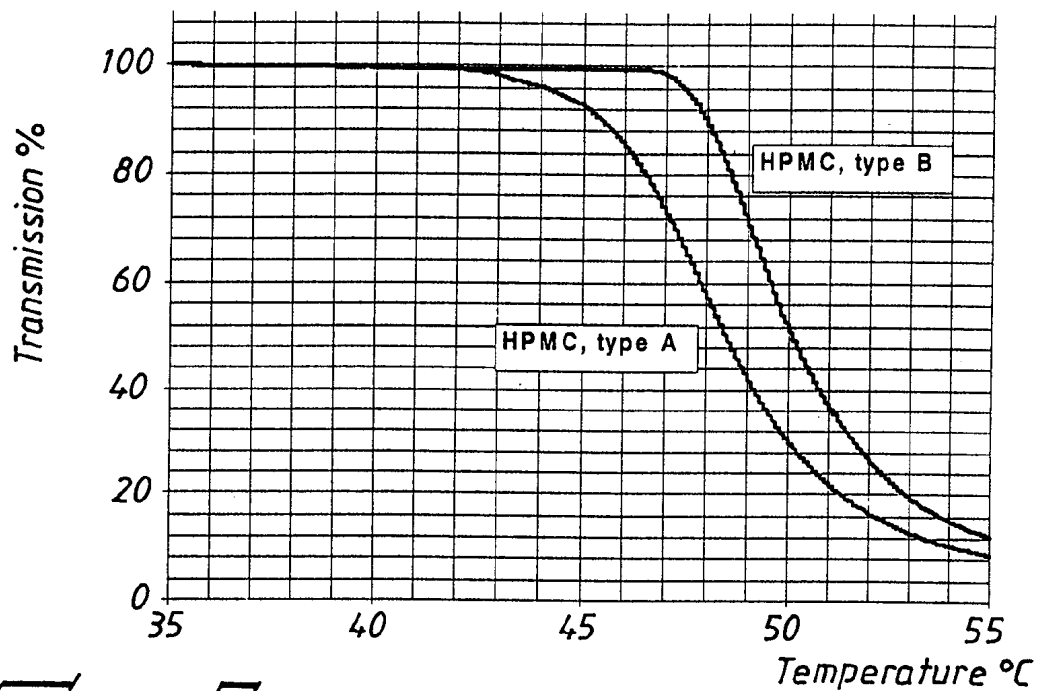
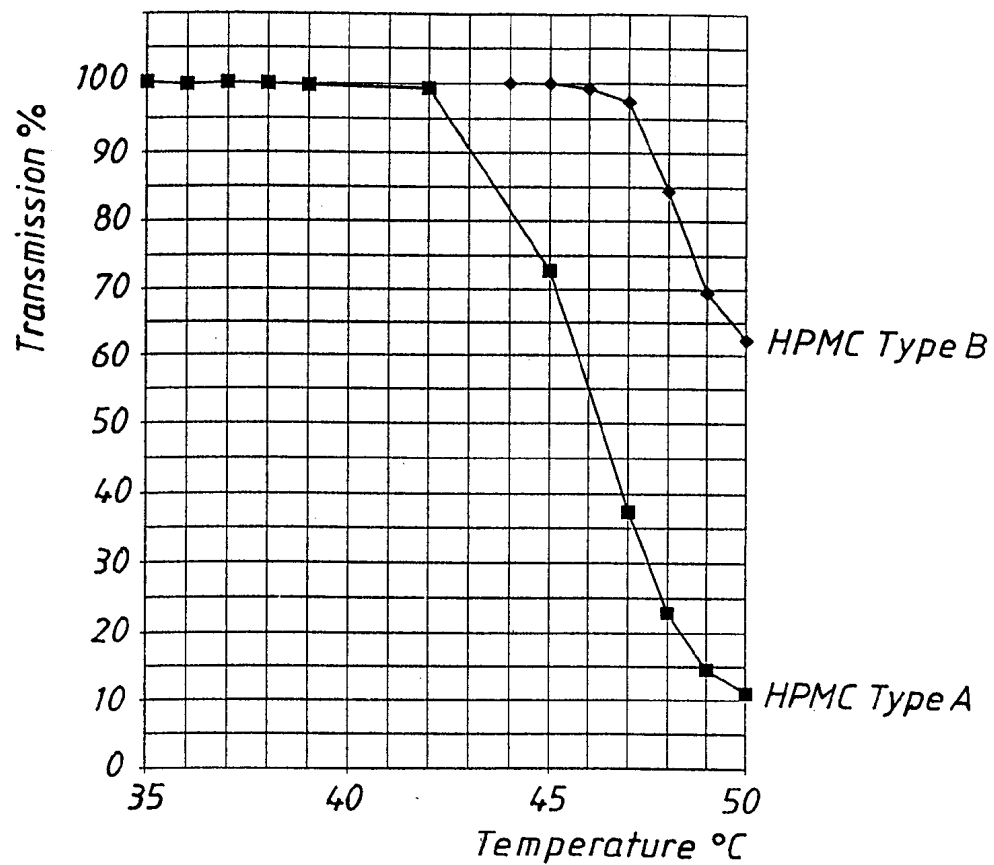
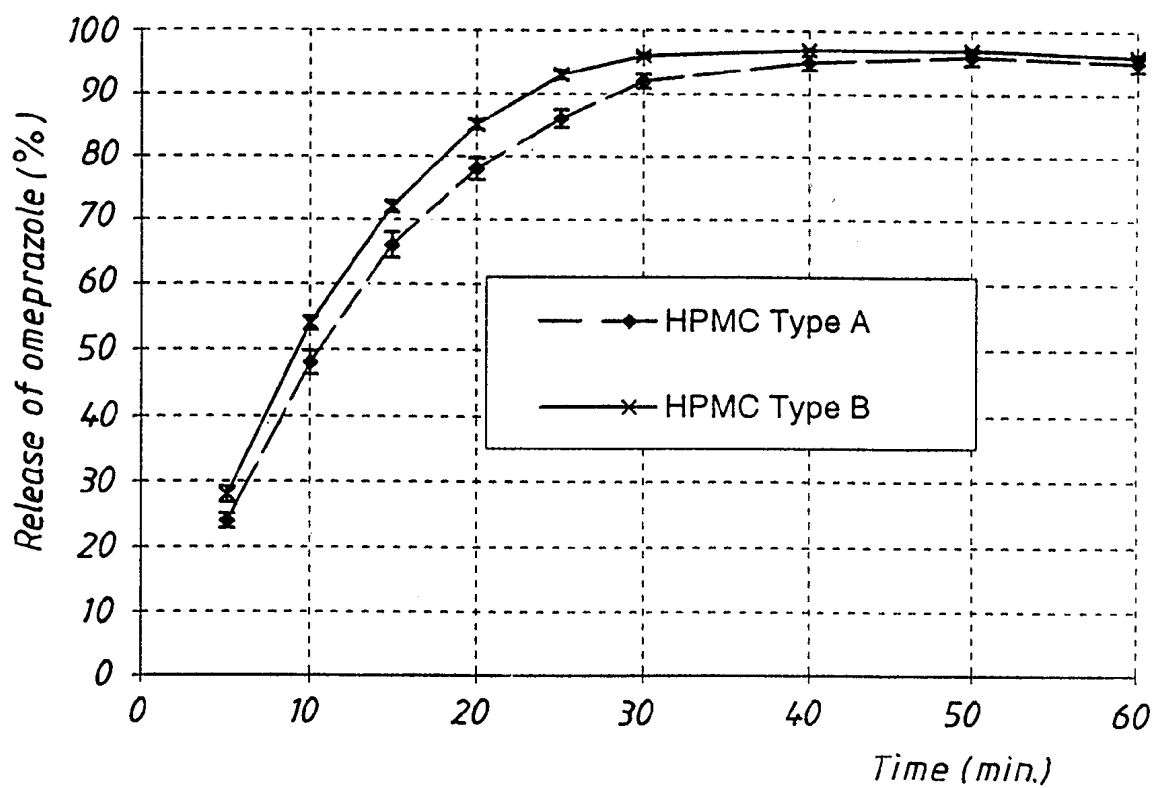


Fig. 2



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Fig. 3



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00922

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/28, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,N0 classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, EMBASE, WPI, CLAIMS, USPATFULL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0247983 A2 (AKTIEBOLAGET HÄSSLE), 2 December 1987 (02.12.87) --	1-19
A	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96) --	1-19
A	US 5372998 A (HIROYASU KOKUBO ET AL), 13 December 1994 (13.12.94), claims -- -----	1-19

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

9 Sept 1998

Date of mailing of the international search report

11-09-1998

Name and mailing address of the ISA/

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00922

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Claim 19 is directed to a method of treatment of the human or animal body by a therapy method practised on the human or animal body /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compositions.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

- The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.

PCT/SE 98/00922

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Information on patent family members

27/07/98

International application No.

PCT/SE 98/00922

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/SE98/00974 <b>(22) International Filing Date:</b> 25 May 1998 (25.05.98) <b>(30) Priority Data:</b> 9702065-5 30 May 1997 (30.05.97) SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> COTTON, Hanna [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). KRONSTRÖM, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MATTSON, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MÖLLER, Eva [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NOVEL FORM OF SOMEPRAZOLE  <b>(57) Abstract</b>  The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2- [[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. <i>S</i> -omeprazole. More specifically, it relates to a novel form of the magnesium salt of the <i>S</i> -enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of <i>S</i> -omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.		

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## NOVEL FORM OF S-OMEPRAZOLE

*Field of the Invention*

The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[  
5 methoxy-3,5-dimethyl-2-pyridinyl)-methy]sulfinyl]-1H-benzimidazole, *i.e.* S-omeprazole.  
More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of  
omeprazole trihydrate. The present invention also relates to processes for preparing such a  
form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing  
it. Furthermore, the present invention also relates to intermediates used in the process, and  
10 their preparation.

*Background of the invention and prior art*

The compound 5-methoxy-2-[[  
15 methoxy-3,5-dimethyl-2-pyridinyl)methy]sulfinyl]-1H-  
benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts  
thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in  
EP 124 495. Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid  
secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be  
used for prevention and treatment of gastric-acid related diseases in mammals and  
20 especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the  
stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers,  
the *R* and *S*-enantiomer of omeprazole, herein referred to as *R*-omeprazole and *S*-  
25 omeprazole. The absolute configurations of the enantiomers of omeprazole have been  
determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt  
form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form  
were found to have *R* and *S* configuration, respectively, and the (+)-enantiomer of the  
magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have *R*

and *S* configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

5 Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

10 WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of *R*- and *S*-omeprazole.

*Brief description of the drawings*

15 Figure 1 shows a X-ray powder diffractogram of the magnesium salt of *S*-omeprazole trihydrate prepared according to the present invention.

Figure 2 shows a X-ray powder diffractogram of the potassium salt of *S*-omeprazole prepared and used in the present application (See examples 2 and 3)

20 Figure 3 shows a X-ray powder diffractogram of a magnesium salt of *S*-omeprazole dihydrate prepared and used in the present application (See example 5)

Figure 4 shows a X-ray powder diffractogram of a magnesium salt of *S*-omeprazole dihydrate which is a polymorph of the dihydrate shown in Figure 3 (See Example 6). This magnesium salt of *S*-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of *S*-omeprazole trihydrate according to the present invention.

25 Figure 5 shows X-ray powder diffractogram of the magnesium salt of *S*-omeprazole prepared according to example A in WO 96/01623 .

*Description of the Invention*

It has surprisingly been found that the magnesium salt of *S*-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of *S*-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of *S*-omeprazole trihydrate from other forms of magnesium salts of *S*-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of *S*-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of *R*-omeprazole. The magnesium salt of *S*-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of *S*-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of *S*-omeprazole and accordingly, the magnesium salt of *S*-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of *S*-omeprazole disclosed in prior art. The compound of the invention is characterized by being

highly crystalline, *i.e.* having a higher crystallinity than any other form of magnesium salt of *S*-omeprazole disclosed in the prior art. With the expression "any other form" is meant anhydrides, hydrates, solvates, and polymorphs or amorphous forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of *S*-omeprazole includes, but  
5 are not limited to, anhydrides, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanولات, and polymorphs or amorphous forms thereof.

The compound of the invention may also be characterized by its unit cell.

10

In a further aspect, the present invention provides processes for the preparation of the magnesium salt of *S*-omeprazole trihydrate which comprises;

a) treating a magnesium salt of *S*-omeprazole of any form, for example prepared according  
15 to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable  
20 time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, *i.e.* results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions  
25 used. The magnesium salt of *S*-omeprazole trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

b) oxidizing 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-  
30 benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the

presence of a base. The oxidation is carried out in an organic solvent, for example toluene or dichloromethane.

The crude product is converted to the corresponding potassium salt by treatment with a potassium source, such as methanolic potassium hydroxide or methanolic potassium  
5 methylate, followed by isolation of the formed salt.

The resulting potassium salt of *S*-omeprazole is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is  
10 initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above.

Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of *S*-omeprazole trihydrate, or any other conventional technique for transforming a potassium salt to the  
15 corresponding magnesium salt can be used and is within the scope of the present invention.

Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of *S*-omeprazole is found to be such a suitable intermediate. The  
20 potassium salt of *S*-omeprazole may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

The compound of the invention, *i.e.* the magnesium salt of *S*-omeprazole trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which  
25 is known per se.

The amount of water in the magnesium salt of *S*-omeprazole trihydrate is determined by thermogravimetric analysis, a technique which is known per se.



The compound of the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

15

Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of *S*-omeprazole trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

20

It is further provided a pharmaceutical composition comprising the magnesium salt of *S*-omeprazole trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of the magnesium salt of *S*-omeprazole trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of *S*-omeprazole trihydrate according to the invention.

30

The compositions of the invention include compositions suitable for peroral or parental administration. The most preferred route is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of *S*-omeprazole trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

In general, a suitable oral dosage form of the compound of the invention may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination preparations comprising the magnesium salt of *S*-omeprazole trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but

are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

5 The examples which follow will further illustrate the preparation of the compound of the invention, according to different process routes and including new intermediates. These examples are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

### Examples

10

#### Example 1

#### ***S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate***

15

Water (157 kg) was added to the wet crystals of the magnesium salt of *S*-omeprazole, prepared according to Example 4, below. The mixture was heated to 38°C with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

20 X-ray powder diffraction analysis was performed on a sample of the crystals prepared above according to standard methods, which can be found in *e.g.* Kitaigorodsky, A. I. (1973), *Molecular Crystals and Molecules*, Academic Press, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H.P. & Alexander, L. E. (1974), *X-Ray Diffraction Procedures*, John Wiley and Sons, New York. The analysis  
25 gave the diffractogram depicted in Figure 1. The main peaks, with positions and relative intensities, have been extracted from the diffractogram in Figure 1 and is given below in table 1. The relative intensities are less reliable and instead of numerical values the following definitions are used.

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)
<1	vw (very weak)

Some additional very weak peaks found in the diffractogram have been omitted from table 1.

Table 1. Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of *S*-omeprazole trihydrate.

<i>d</i> -value / Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

## Example 2

***S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt***

5

A solution of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.8 mmol) in toluene (70 ml) was heated to 50°C and water (0.05 ml, 2.8 mmol) and D-(-)-diethyl tartrate (2.02 g, 9.82 mmol) were added. The reaction mixture was stirred for 20 minutes. Titanium(IV)isopropoxide (1.34 g, 4.68 mmol) was added and the reaction mixture was stirred for 45 minutes. The mixture was cooled to 30°C and diisopropylethylamine (0.91 g, 7.01 mmol) was added followed by cumene hydroperoxide (9.52 g, 51.89 mmol). The resultant mixture was stirred at 30°C for 3 hours. Methanol (40 ml) was added followed by potassium hydroxide (3.05 g, 46.8 mmol) in methanol (30 ml). Seed crystals were added and the reaction mixture was stirred at 35°C overnight. The precipitated product was filtered off, washed with methanol and toluene and dried in vacuo. Yield: 9.74 g (54%).

10

15

## Example 3

20

***S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt***

Water (157.6 µl) was added to a solution of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene (370 ml; 211.5 g/l) with a water content of 0.031% (w/w), followed by addition of D-(-)-diethyl tartrate (8.55 ml). The solution was heated to 50°C and stirred at this temperature for 20 minutes.

25

Titanium(IV)isopropoxide (7.15 ml) was added and reaction was left at 50°C for 45 minutes. The temperature was lowered to 30°C and diisopropylethylamine (6.2 ml) was added. Cumene hydroperoxide was added at an appropriate speed to maintain the temperature from 28°C to 34°C. The temperature was raised to 35°C after 2 hours and

30

potassium methoxide (24.55 g) in methanol (222 ml) was added. The mixture was filtered after 14 hours and the crystals were washed with methanol:toluene (240 ml; 1:1) and methanol (120 ml) and dried. Yield: 79 g (74%), ee > 99.9%.

$[\alpha]_D^{20} = +28.7^\circ$  (c = 1%, water); Assay: 89% is S-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (11% is methanol).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>, δ ppm): 2.23 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 4.40 (d, 1H), 4.78 (d, 1H), 6.58 (dd, 1H), 7.00 (d, 1H), 7.35 (d, 1H), 8.25 (s, 1H).

10 The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in Figure 2 and given below in Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

15 Table 2. Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

$$\alpha_1 = 1.54060 \text{ \AA}$$

## Example 4

***S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt***

5

Methanol (148 kg) was added to S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (71 kg, methanol content = 13%).

MgSO<sub>4</sub> x 7 H<sub>2</sub>O (40 kg) was added to the mixture while stirring. After 70 minutes the mixture was filtered and the filtrate was washed with methanol (46 kg). The solution was concentrated to a volume of 100 liter, acetone (253 kg) was added and the resulting mixture was left for 4 hours. The precipitated product was filtered off, washed with acetone and water. The wet crystals were immediately used as is described in Example 1.

## Example 5

15

***S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate***

5.0 g of the moist product from Example 4 with an approximate dry content of 74%, was dried in vacuum at 35 °C over night to yield 3.58 g (2.68 mmol) of S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named Form B.

The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in Figure 3 and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.



Table 3. Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of *S*-omeprazole dihydrate, Form B.

d-value / Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m
8.1	s
11.0	m
11.8	m
14.9	vs

5 *Conversion of magnesium salt of S-omeprazole dihydrate to trihydrate*

This material was subsequently processed to S-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate according to the procedure described for the moist substance in Example 1.

## Example 6

***S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate***

5

A methanolic solution of S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt was prepared as is described in Example 4. Such a solution of S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt (1.86g) in 5 ml methanol was  
10 concentrated by evaporation until 1.58 ml methanol remained. Then, a mixture of 1.6 ml water and 6.32 ml acetone was added. The solution was allowed to crystallize during 26 h at room temperature. The resulting crystals were filtered off and dried at 40 °C under reduced pressure giving 1.17 g of S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named form A.

15

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in Figure 4 and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

20 Table 4. Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form A.

d-value / Å	Relative Intensity
3.04	s
3.14	s
3.18	m
4.05	s
4.19	s
4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

## Example 7

5 *S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate*

22,0 g (29,1 mmol) of S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt was dissolved in 40 mL of water. The solution was seeded with 0,11 g (0,1 mmol) S-5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. 22 mL (69,6 mmol) of MgSO<sub>4</sub> (aq) was added under a 3 h period. The slurry was filtered off and the precipitate was elutriated in water for approximately 30 minutes and the crystals were filtered off and dried (35 °C, vacuum).

Yield: 9,15 g (11,6 mmol; 80%). The substance had a purity (HPLC):99,8 area%, Mg content: 3,40 % (w/w) and ee: 99,8%.

The product was analyzed using X-ray powder diffraction and the result complies with  
5 Figure 1 and Table 1.

#### Reference Example A

#### *S-5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H- 10 benzimidazole magnesium salt*

(The method used is in accordance with the method described in Example A in WO 96/01623)

15 Magnesium (0.11g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40°C with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(-)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the  
20 magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with  
25 an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the  
30 crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the

optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy.  $[\alpha]_D^{20} = -131.5^\circ$  (c=0.5%, methanol).

5

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in Figure 5 and given below in Table 5. Some additional very weak peaks found in the diffractograms have been omitted from Table 5.

Table 5. Positions and intensities of the major peaks in the XRP-diffractogram shown in Figure 5.

<i>d</i> -value / Å	<i>Relative Intensity</i>
<b>2.90</b>	S
<b>3.41</b>	S
<b>3.90</b>	S
<b>4.13</b>	S
<b>4.79</b>	VS
<b>5.00</b>	VS
<b>5.4</b>	VS
<b>5.7</b>	S
<b>6.3</b>	S
<b>6.8</b>	S
<b>7.8</b>	S
<b>8.4</b>	VS
<b>10.8</b>	S
<b>12.2</b>	S
<b>15.1</b>	VS

## Claims.

1. The magnesium salt of *S*-omeprazole trihydrate.
- 5 2. The magnesium salt of *S*-omeprazole trihydrate according to claim 1, characterized by being highly crystalline.
3. The magnesium salt of *S*-omeprazole trihydrate according to claim 1, characterized by the following major peaks in its X-ray powder diffractogram.

10

<i>d</i> -value / Å	Relative Intensity
<b>2.67</b>	m
<b>2.79</b>	m
<b>3.27</b>	m
<b>3.52</b>	s
<b>3.82</b>	s
<b>3.96</b>	vs
<b>4.14</b>	m
<b>5.2</b>	m
<b>5.6</b>	m
<b>6.7</b>	vs
<b>6.9</b>	s
<b>8.3</b>	w
<b>16.6</b>	vs

4. A process for the preparation of the magnesium salt of *S*-omeprazole trihydrate according to any of claims 1-3 which comprises treating a magnesium salt of *S*-omeprazole of any other form with water.

15

5. A process for the preparation of the magnesium salt of *S*-omeprazole trihydrate according to any of claims 1-3 which comprises the following steps;

- a) mixing a potassium salt of *S*-omeprazole with an organic solvent;
- b) converting the potassium salt of *S*-omeprazole into a corresponding magnesium salt of *S*-omeprazole by treating the said potassium salt with a magnesium source;
- c) precipitating the magnesium salt of *S*-omeprazole by addition of a non-solvent;
- d) isolating the obtained magnesium salt of *S*-omeprazole;
- e) treating the obtained magnesium salt of *S*-omeprazole with water; and
- f) isolating and drying the magnesium salt of *S*-omeprazole trihydrate thus obtained.

6. A process according to claim 5 wherein said organic solvent used in step a) is methanol.

7. A process according to any of claims 5-6, wherein the said non-solvent used in step c) is acetone.

8. A process according to claim 5 wherein steps a) to e) are replaced by the single step;  
i) converting the potassium salt of *S*-omeprazole into a corresponding magnesium salt of *S*-omeprazole by treating said potassium salt with a magnesium source in water.

9. A process according to any of claims 5-8, wherein the said magnesium source used in step b) of claims 5-7 or step i) of claim 8 is magnesium sulfate.

10. A process for the preparation of a potassium salt of *S*-omeprazole to be used in any of claims 5-9, which process comprises the following steps;

- a) oxidizing 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole into *S*-omeprazole in an organic solvent;
- b) converting the *S*-omeprazole into the corresponding potassium salt of *S*-omeprazole by treating said *S*-omeprazole with a potassium source ;
- c) isolating the potassium salt of *S*-omeprazole thus obtained.



11. A process according to claim 10, wherein said organic solvent used in step a) is toluene.

s 12. A process according to any of claims 10-11, wherein said potassium source used in step b) is methanolic potassium methoxide or methanolic potassium hydroxide.

13. Potassium salt of *S*-omeprazole prepared according to claim 10 characterized by the following peaks in its X-ray powder diffractogram.

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

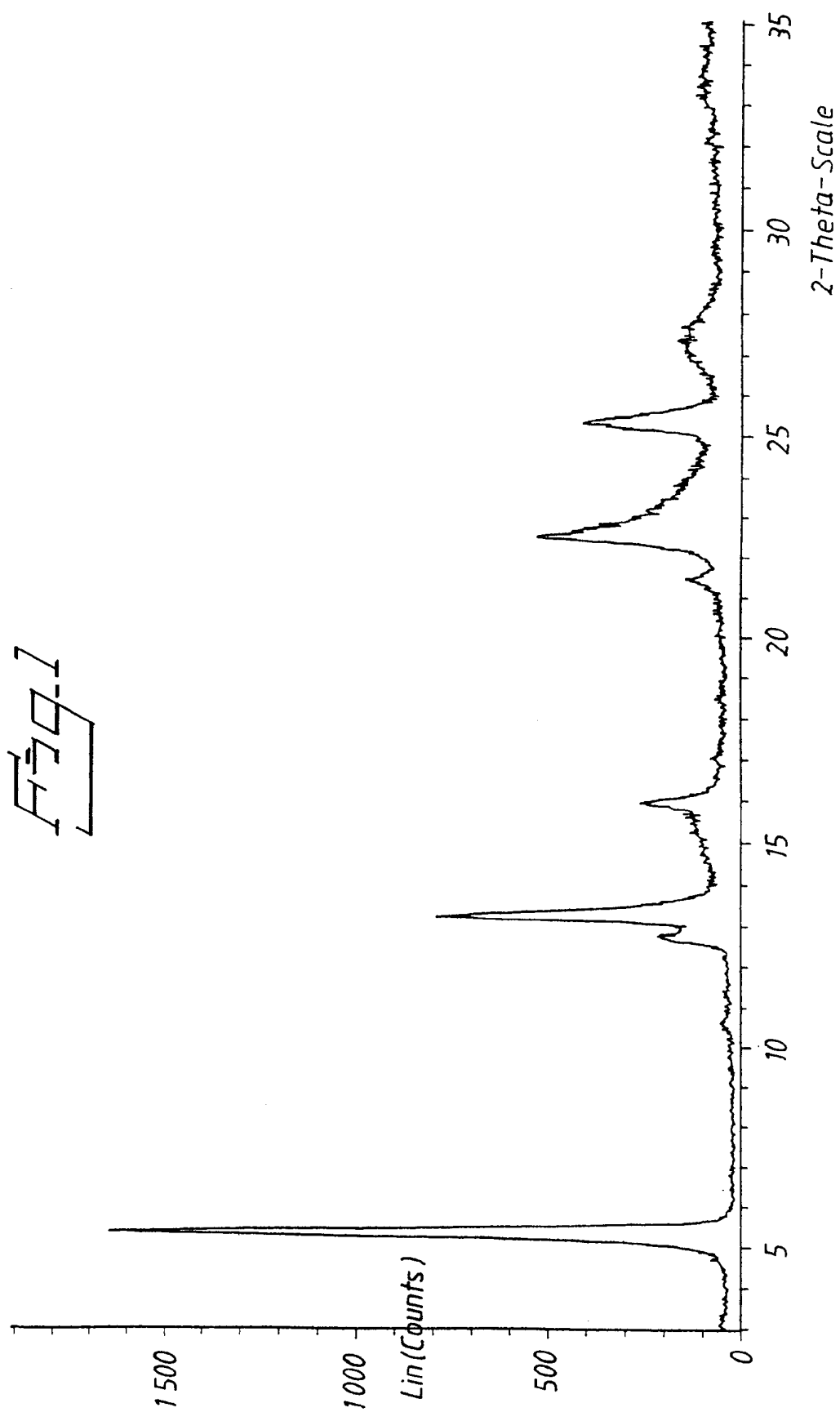
$$\alpha_1 = 1.54060 \text{ Å}$$

14. A pharmaceutical composition comprising the magnesium salt of *S*-omeprazole trihydrate according to any of claims 1-3 as active ingredient in association with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients.

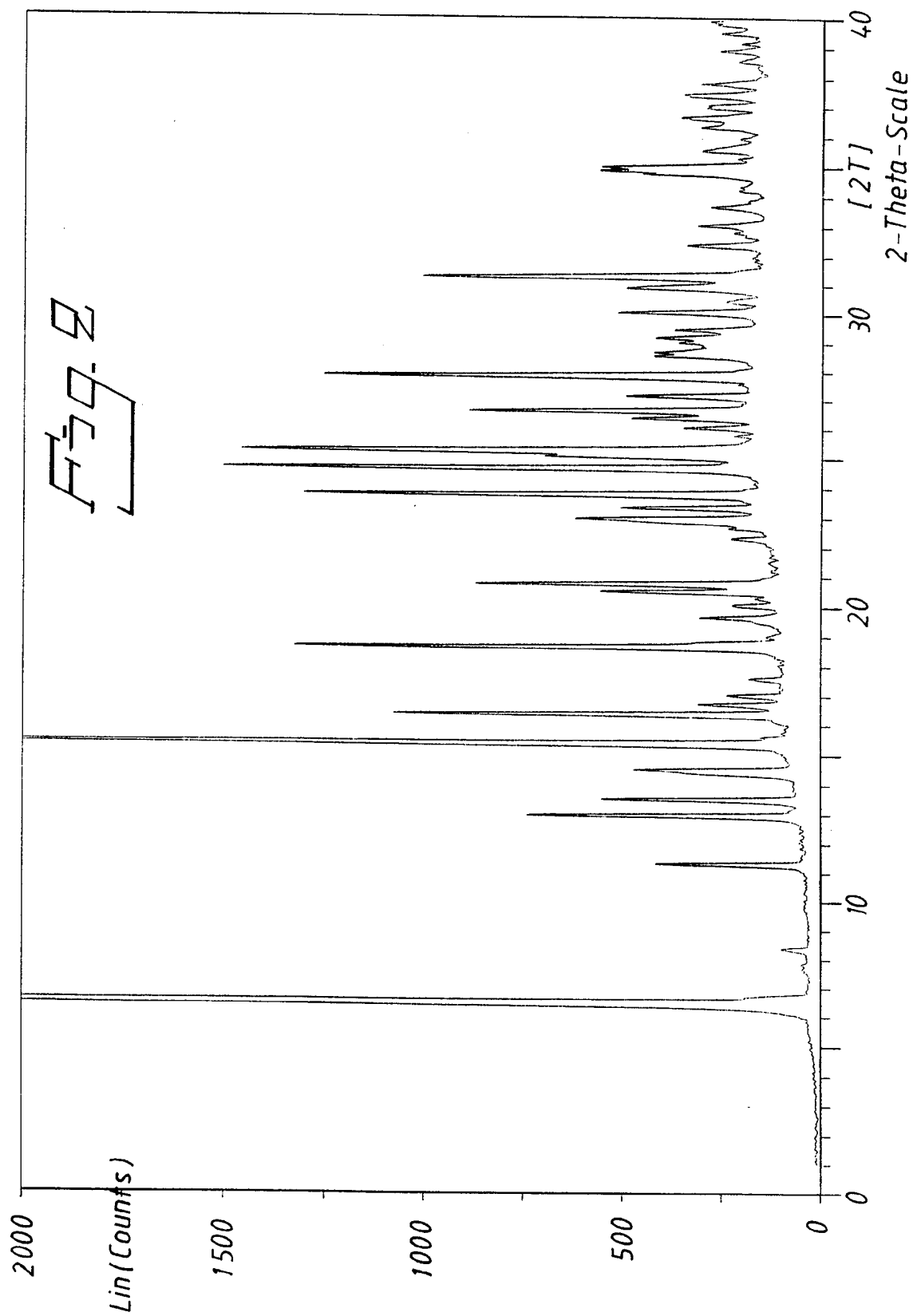
5 15. Use of the magnesium salt of *S*-omeprazole trihydrate defined in any of claims 1-3 in the manufacture of a medicament for use in the treatment of a gastric acid related condition.

10 16. A method of treating a gastric acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of *S*-omeprazole trihydrate defined in any of claims 1-3.

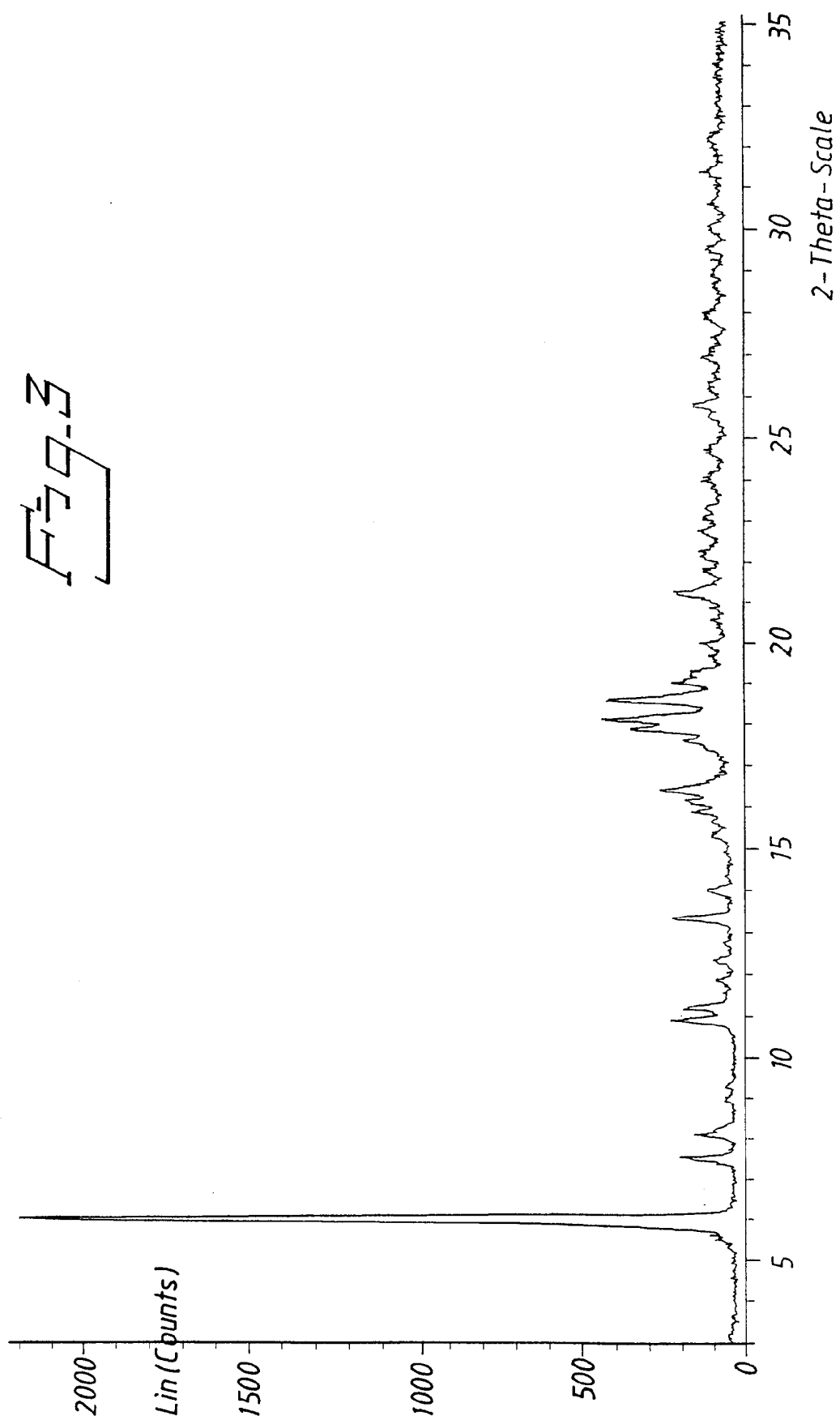
1 / 5



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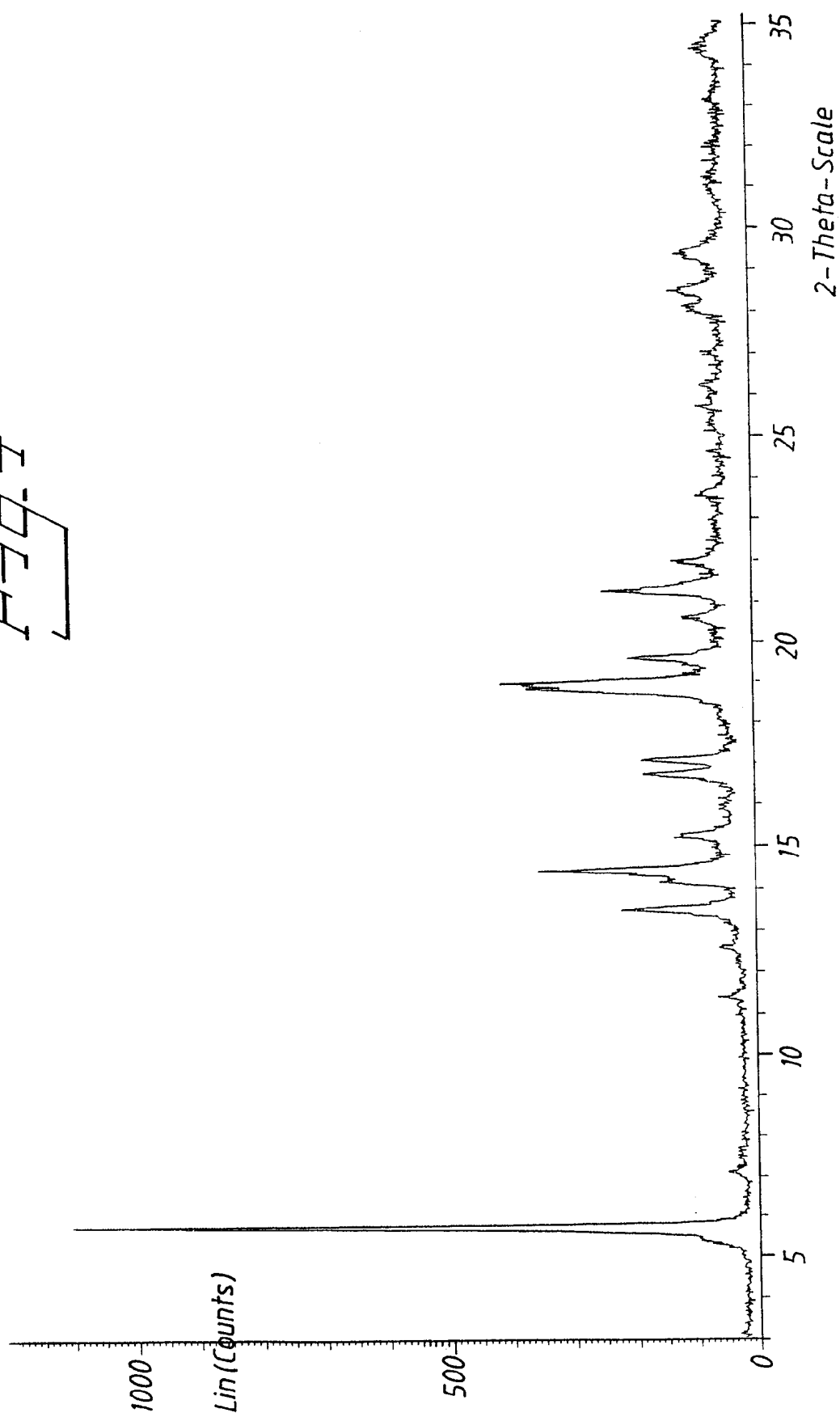


3 / 5

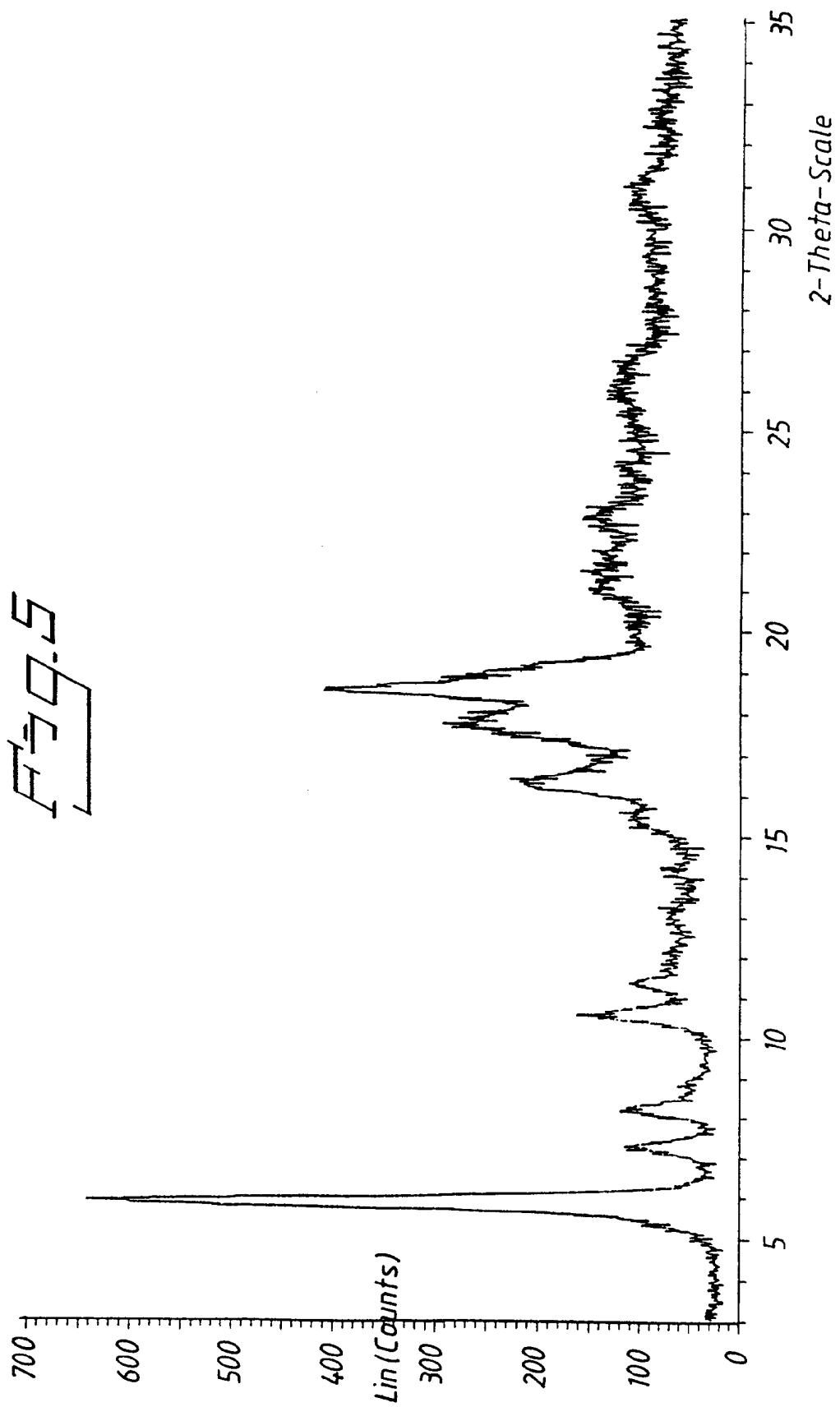


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Fig. 4



5 / 5





## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00974

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96)  --	1-15
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.94)  -- -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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25 August 1998

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00974

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy,  
see rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

- The additional search fees were accompanied by the applicant's protest.  
No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.

PCT/SE 98/00974

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 401/12, A61K 31/44</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/54171</b> <b>(43) International Publication Date:</b> 3 December 1998 (03.12.98)
<b>(21) International Application Number:</b> PCT/SE98/00974 <b>(22) International Filing Date:</b> 25 May 1998 (25.05.98) <b>(30) Priority Data:</b> 9702065-5      30 May 1997 (30.05.97)      SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> COTTON, Hanna [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). KRONSTRÖM, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MATTSON, Anders [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). MÖLLER, Eva [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> NOVEL FORM OF S-OMEPRAZOLE  <b>(57) Abstract</b> <p>The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2- [[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.</p>		

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<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 401/12, A61K 31/44</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/00380</b> <b>(43) International Publication Date:</b> 7 January 1999 (07.01.99)
<b>(21) International Application Number:</b> PCT/SE98/01124 <b>(22) International Filing Date:</b> 11 June 1998 (11.06.98) <b>(30) Priority Data:</b> 9702483-0                      27 June 1997 (27.06.97)                      SE <b>(71) Applicant (for all designated States except US):</b> ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> GUSTAVSSON, Anders [SE/SE]; (SE). KJELLBOM, Kristina [SE/SE]; (SE). YMÉN, Ingvar [SE/SE]; Astra Production Chemicals AB, S-151 85 Södertälje (SE). <b>(74) Agent:</b> ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> OMEPRAZOLE SODIUM SALT  <b>(57) Abstract</b> <p>This invention relates to a novel form of the sodium salt of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, known under the generic name of omeprazole sodium salt. This invention also relates to processes for its preparation of omeprazole sodium form B which is thermodynamically stable, as well as pharmaceutical compositions containing it and its use in the treatment of gastrointestinal disorders.</p>		

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## OMEPRAZOLE SODIUM SALT

Field of the invention

5 This invention relates to a novel form of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel form of the sodium salt of omeprazole, namely a well-defined omeprazole sodium monohydrate salt, hereinafter referred to as omeprazole sodium form B, and its use in the treatment of gastrointestinal disorders, pharmaceutical  
10 compositions containing it and preparation thereof.

Background of the invention and prior art

The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-  
15 benzimidazole having the generic name omeprazole, as well as therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole, such as the sodium salt, are disclosed in EP 124 495. The omeprazole sodium salt produced according to examples 1 and 2 of EP 124 495 is a mixture of crystal forms and amorphous material. One of the crystal forms present in this mixture, hereinafter referred to as  
20 omeprazole sodium form A, is a hydrate with one to two water molecules, of which one water molecule is strongly bound in the crystal structure while the other is easily removed by drying. The resulting dried substance containing one strongly bound water molecule is very hygroscopic and absorbs water rapidly under normal conditions.

25 Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.



### Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of omeprazole sodium form B.

Figure 2 is an X-ray powder diffractogram of omeprazole sodium form A.

- 5 Figure 3 is an X-ray powder diffractogram of omeprazole sodium prepared according to prior art.

### Description of the invention

- 10 It has surprisingly been found that the sodium salt of omeprazole exists in a number of different crystal forms. It is an object of the present invention to provide a well-defined, thermodynamically stable at ambient temperature, and industrially useful form of omeprazole sodium, namely omeprazole sodium form B. Another object of the present invention is to provide a process for the preparation of omeprazole sodium form B,
- 15 substantially free from other forms of the sodium salt of omeprazole. X-ray powder diffraction (XRPD) is used as a method of differentiating omeprazole sodium form B from other forms of the sodium salt of omeprazole.

- It has been found that the sodium salt of omeprazole may crystallize in at least two
- 20 different crystal forms, of which omeprazole sodium form B is one. One other form is omeprazole sodium form A with one to two moles of water. Omeprazole sodium form A is one of the crystal forms present in the mixture of crystal forms and amorphous material obtained in example 1 and example 2 in EP 124 495. However, there is no omeprazole sodium form B present in the mixture of forms obtained when preparing omeprazole
- 25 sodium salt as described in either example 1 or example 2 in EP 124 495.

- Omeprazole sodium form B is a crystalline form exhibiting advantageous properties, such as being well-defined, stable, and being a true monohydrate crystal form. Omeprazole sodium form B is thermodynamically more stable than omeprazole sodium form A.
- 30 Omeprazole sodium form B is essentially non-hygroscopic and can therefore in industrial

processes, such as pharmaceutical manufacturing processes, be charged in a fixed amount in contrast to omeprazole sodium form A which must be charged in amounts calculated from a recent assay of omeprazole or indirectly from a recent assay of its water content. Other advantages include easier preparation and higher reproducibility between batches.

5 This is especially important in production scale and leads to a higher production capacity.

Omeprazole sodium form A, which is thermodynamically unstable, can under certain storing conditions be completely or partly converted to omeprazole sodium form B. Omeprazole sodium form B is thereby characterized in being thermodynamically more

10 stable than omeprazole sodium form A and any other form of omeprazole sodium prepared according to prior art. Omeprazole sodium form B is further characterized as being essentially non-hygroscopic.

With the expression "any other form" is meant anhydrides, hydrates, solvates and

15 amorphous materials, including polymorphs disclosed in the prior art. Examples of any other forms of sodium salts of omeprazole includes, but are not limited to, anhydrides, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates and polymorphs or amorphous forms thereof.

20 Omeprazole sodium form B is characterized by the positions and intensities of the peaks in the X-ray powder diffractogram, as well as by the unit cell parameters which have been calculated from the peak positions. The corresponding data for omeprazole sodium form A are totally different, whereas form B is easily distinguishable from form A.

Omeprazole sodium form B according to the present invention is characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

d-value/Å	relative intensity	d-value/Å	relative intensity
9.8	vs	3.37	w
7.8	vw	3.25	vw
6.7	s	3.17	vw
6.5	s	3.14	w
6.2	vw	3.12	m
5.9	m	3.05	w
5.8	vw	2.99	w
5.4	w	2.98	m
5.1	w	2.91	m
4.6	m	2.89	m
4.5	m	2.79	vw
4.3	s	2.62	vw
4.1	m	2.59	vw
3.96	m	2.50	vw
3.92	m	2.45	vw
3.71	s	2.40	vw
3.60	w	2.37	vw
3.43	vw	2.28	vw

Omeprazole sodium form B according to the present invention is characterized by having a monoclinic unit cell with parameters

$$a = 15.09 \text{ Å}, b = 12.83 \text{ Å}, c = 9.82 \text{ Å}, \beta = 94.4^\circ.$$

According to the invention there is further provided a process for the preparation of omeprazole sodium form B as well as a process for the preparation of omeprazole sodium form A.

5 Omeprazole sodium form B can also be characterized by FT-IR.

Omeprazole sodium form B is prepared by treating omeprazole with an aqueous base,  $\text{Na}^+ \text{B}^-$ , wherein Na denotes sodium and B denotes hydroxide or alkoxide, in an appropriate solvent, such as isopropanol optionally containing some water, at ambient temperature.

10 Once the mixing has taken place the total mixture may be agitated, for example stirred, for a further period of time, *e.g.* about 0-2 hours, at ambient temperature. The crude mixture may optionally be filtered at this stage. Seeds of omeprazole sodium form B may be added to the crystallization solution in order to induce the crystallization. The slurry is thereafter further agitated for a time period of about 10-24 h to ensure as complete crystallization as possible. It is also possible to cool the mixture in order to complete the crystallization and thereby improving the yield. The omeprazole sodium form B is thereafter separated, for example by filtration or centrifugation, followed by washing with an appropriate solvent, preferably the same solvent as used above, and thereafter dried to constant weight.

20 Omeprazole sodium form B may also be prepared by recrystallizing the sodium salt of omeprazole of any form, or mixtures thereof, in an appropriate solvent such as ethanol or isopropanol, optionally containing some water.

The omeprazole sodium form B obtained according to the present invention is substantially free from other forms of sodium salts of omeprazole, such as omeprazole sodium form A.

25 The compound of the invention, *i.e.* omeprazole sodium form B, prepared according to the present invention is analyzed, characterized and differentiated from omeprazole sodium form A by X-ray powder diffraction, a technique which is known per se. Another suitable

technique to analyze, characterize and differentiate omeprazole sodium form B from omeprazole sodium form A is by conventional FT-IR.

The amount of water in omeprazole sodium form B and omeprazole sodium form A is  
5 determined by thermogravimetric analysis, a technique which is known per se. The water content can also be determined by Karl Fischer.

Omeprazole sodium form B is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid  
10 related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The  
15 compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may  
20 also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of omeprazole sodium form B according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include  
25 capsules, tablets, dispersions, solutions, suspensions and the like. Omeprazole sodium form B is, because of it being highly soluble in water, especially suitable for parenteral formulations, such as for intravenous administration.

According to the invention there is further provided a pharmaceutical composition  
30 comprising omeprazole sodium form B, as active ingredient, in association with a

pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of omeprazole sodium form B in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of omeprazole sodium form B.

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

Combination therapies comprising omeprazole sodium form B and other active ingredients in separate dosage forms may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of omeprazole sodium form B in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable dose range for parental administration is from 10 mg to 300 mg, and preferably from 20 mg to 80 mg.

A suitable oral dosage form may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

- 5 The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.
- 10 The examples which follow will further illustrate the preparation of the compound of the invention, i.e. omeprazole sodium form B, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

### Examples

15

#### Example 1

##### *Preparation of omeprazole sodium form B from omeprazole*

- 20 120 gram of omeprazole, 480 ml of isopropanol and 13.2 gram of NaOH(s) dissolved in 26.7 gram of water, was added to a 3-necked glass vessel. The slurry was stirred for an additional 40 minutes at ambient room temperature. The obtained solution was filtered through a clarifying filter and the filter was washed with 20 ml of isopropanol. The isopropanol wash was combined with the previous isopropanol solution containing the
- 25 product. The solution was seeded with 6 gram of omeprazole sodium form B in 25 ml of isopropanol. The slurry was stirred for an additional 25 hours and the product was filtered and dried at 40°C.

Yield 84.5 %.

Example 2*Preparation of omeprazole sodium form B from omeprazole sodium form A*

5 30 gram of omeprazole sodium form A, prepared according to example 3 below, and 25 ml of ethanol was added to a 3-necked glass vessel. The slurry was seeded with omeprazole sodium form B and then stirred for an additional 24 hours at room temperature. The product was then filtered and dried at 50°C.

Yield: 80%

10

Example 3*Preparation of omeprazole sodium form A from omeprazole*

15

14.8 kg sodium hydroxide was dissolved in 42 l water in a separate vessel.

120 kg omeprazole was added to 927 l isopropanol in a 4000 l glass lined reactor. The aqueous sodium hydroxide was charged to the slurry. Omeprazole was dissolved and the  
20 clear solution was filtered in a closed pressure filter to a 1200 l glass lined reactor. The solution was heated and 228 l methanol was charged at 50 °C to initiate the crystallization. The batch was seeded with a slurry of 1.2 kg omeprazole sodium methanol wet in isopropanol. The solution was cooled from 51 °C to - 8 °C. The formed slurry was kept at - 8 to - 9 °C for 4 hours with moderate stirring. Centrifuged substance was flushed with a  
25 cool mixture of isopropanol and methanol, 76 l and 20 l respectively, and then dried in a rotary dryer at approximately 35 mbar with a jacket temperature of 65 °C. Dried substance was de-lumped in a mill.

Yield: 126.0 kg omeprazole sodium methanol wet.

30



A sample of the omeprazole sodium methanol wet (32.3 kg) was charged into a rotary dryer. An equilibration process with steam in order to remove methanol was performed at 39 - 87 mbar and with a jacket temperature of 50 °C. The equilibration process took 3 days. Equilibrated substance was de-lumped in a mill.

5 Yield: 25.7 kg

#### Example 4

*Characterization of omeprazole sodium form B and omeprazole sodium form A using*  
10 *X-ray powder diffraction (XRPD)*

X-ray powder diffraction analysis was performed according to standard methods which can be found in e.g. Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and  
15 Sons, New York. The unit cell parameters for form A and B have been calculated from the X-ray powder diffractograms using the program "TREOR" by Werner, P.-E., Eriksson, L. And Westdahl, M., J. Appl. Crystallogr. 18 (1985) 367 - 370. The fact that the positions of all peaks in the diffractograms for form A and form B may be calculated using the respective unit cell parameters, proves that the unit cells are correct and that the  
20 diffractograms are indicative of the pure forms. The diffractogram of omeprazole sodium form B, prepared according to Example 1 in the present application, is shown in Figure 1 and the diffractogram of omeprazole sodium form A, prepared according to Example 3, is shown in Figure 2.

25 The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractograms for form A, form B and from the diffractogram obtained from material produced according to prior art, and are given in Table 1. In this table the unit cell parameters for forms A and B are also given. The relative intensities are less reliable and instead of numerical values the following definitions are used;

	% Relative Intensity	Definition
	25-100	vs (very strong)
	10-25	s (strong)
	3-10	m (medium)
5	1-3	w (weak)
	<1	vw (very weak)

Some additional very weak peaks found in the diffractograms have been omitted from table 1.

10

#### Reference Example A

*Preparation of omeprazole sodium according to prior art in accordance with the method described in Example 2 in EP 124 495*

15

Omeprazole (1300 g; 3.77 mol) was added under vigorous mechanical stirring to a mixture of tetrahydrofurane (13 L) and 50% aqueous NaOH (296 g, 3.7 mol) and stirring was continued for 45 min. Trichloroethylene (5.7 L) was added and stirring was continued over night at room temperature. The mixture was cooled to +5°C and then stirred for 3 h. The precipitate was filtered off and the filter cake was washed with trichloroethylene (5 L) and dried under reduced pressure at 50°C giving omeprazole sodium salt (1314 g, 95%), m.p. 208-210 °C.

20

The product was analyzed using X-ray powder diffraction and gave the diffractogram depicted in Figure 3 and given above in Table 1. Some additional very weak peaks found in the diffractograms have been omitted from Table 1.

25

Table 1. X-ray powder diffraction data for omeprazole sodium form A, form B and according to prior art. Only peaks below  $2\theta = 40^\circ$  have been included.

All peaks noted for form A and form B can be indexed with the unit cells given below.

- 5 Unit cell form A:  $a = 15.757 (3) \text{ \AA}$       Unit cell form B:  $a = 15.086 (6) \text{ \AA}$   
 $b = 8.126 (1) \text{ \AA}$        $b = 12.835 (4) \text{ \AA}$   
 $c = 15.671 (6) \text{ \AA}$        $c = 9.815 (3) \text{ \AA}$   
 $\beta = 94.21 (2)^\circ$        $\beta = 94.41 (3)^\circ$

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/ $\text{\AA}$	Relative intensity	d-value/ $\text{\AA}$	relative intensity	d-value/ $\text{\AA}$	Relative intensity
				17.8	vw
15.6	vs	9.8	vs	15.5	vs
				13.9	vw
				10.2	vw
				8.9	m
7.9	m	7.8	vw	8.0	m
7.2	m	6.7	s	7.2	m
				6.9	w
6.8	w	6.5	s	6.8	w
6.6	vw	6.2	vw		
6.5	w	5.90	m	6.5	vw
				6.4	vw
				6.2	vw
				5.91	vw
				5.83	w
				5.52	vw

Table 1, continued

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/Å	Relative intensity	d-value/Å	relative intensity	d-value/Å	Relative intensity
5.35	vw	5.76	vw	5.37	w
5.20	s	5.36	w	5.21	w
				5.15	m
				4.81	vw
4.70	vw	5.12	w	4.70	vw
				4.63	vw
4.40	vw	4.57	m	4.40	vw
4.29	vw	4.46	m		
				4.27	vw
4.17	vw	4.29	s	4.17	vw
3.935	s	4.11	m	3.938	w
				3.846	vw
3.831	w	3.963	m		
3.744	w	3.920	m	3.748	vw
				3.711	vw
3.611	w	3.713	s	3.610	vw
3.543	w	3.601	w	3.545	w
3.522	w	3.431	vw	3.519	vw
3.488	w	3.375	w		
				3.464	vw
3.411	vw	3.254	vw	3.410	vw
				3.304	vw
				3.256	vw
				3.151	vw

Table 1, continued

Omeprazole sodium form A		Omeprazole sodium form B		Omeprazole sodium according to prior art	
d-value/Å	Relative intensity	d-value/Å	relative intensity	d-value/Å	Relative intensity
3.125	m	3.173	vw	3.125	vw
				3.079	vw
3.021	vw	3.137	w	3.026	vw
2.919	w	3.119	m	2.911	vw
				2.854	vw
2.833	w	3.050	w		
				2.775	vw
2.676	vw	2.993	w		
2.626	vw	2.980	m		
2.606	vw	2.906	m	2.601	vw
				2.553	vw
2.534	vw	2.892	m		
2.425	vw	2.793	vw	2.430	vw
		2.624	vw		
		2.589	vw		
		2.499	vw		
		2.447	vw		
		2.402	vw		
		2.372	vw		
		2.283	vw		

## CLAIMS

1. Omeprazole sodium form B, characterized in being thermodynamically stable.
- 5 2. Omeprazole sodium form B, characterized in being essentially non-hygrosopic.
3. Omeprazole sodium form B according to claim 1 or claim 2, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values and intensities;

d-value/Å	relative intensity	d-value/Å	relative intensity
9.8	vs	3.37	w
7.8	vw	3.25	vw
6.7	s	3.17	vw
6.5	s	3.14	w
6.2	vw	3.12	m
5.9	m	3.05	w
5.8	vw	2.99	w
5.4	w	2.98	m
5.1	w	2.91	m
4.6	m	2.89	m
4.5	m	2.79	vw
4.3	s	2.62	vw
4.1	m	2.59	vw
3.96	m	2.50	vw
3.92	m	2.45	vw
3.71	s	2.40	vw
3.60	w	2.37	vw
3.43	vw	2.28	vw

4. Omeprazole sodium form B according to any of claims 1-3, characterized by having a monoclinic unit cell with parameters

$$a = 15.09 \text{ \AA}, b = 12.83 \text{ \AA}, c = 9.82 \text{ \AA}, \beta = 94.4^\circ.$$

5 5. A process for the preparation of omeprazole sodium form B as defined in any of claims 1-4, which includes the step of;

- a) preparing the sodium salt of omeprazole by addition of an aqueous base to omeprazole in a solvent mixture comprising an alcohol and water,
- b) allowing the solution to crystallize, optionally using omeprazole sodium form B to  
10 induce crystallization;, and
- c) isolating the omeprazole sodium form B thus obtained.

6. A process according to claim 5, wherein said aqueous base used in step a) is sodium hydroxide.

15

7. A process according to any of claims 5-6, wherein said alcohol used in step a) is isopropanol.

8. A process for the preparation of omeprazole sodium form B as defined in any of claims  
20 1-4, comprising the steps of;

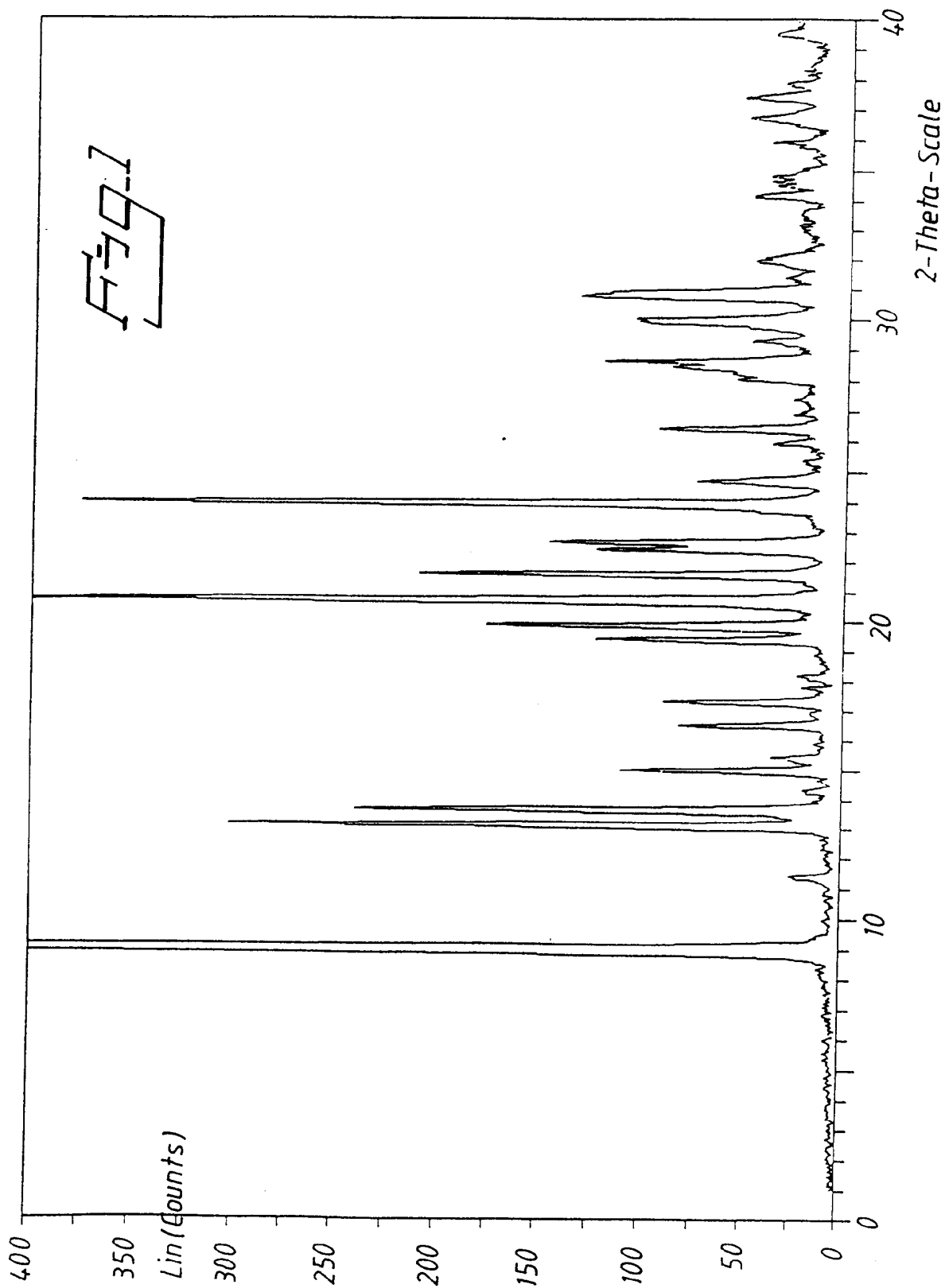
- a) dissolving omeprazole sodium of any form, or a mixture of any forms, in a solvent mixture comprising alcohol and water;
- b) allowing the solution to crystallize, optionally using omeprazole sodium form B to induce crystallization, and
- 25 c) isolating the omeprazole sodium form B thus obtained.

9. A pharmaceutical formulation comprising omeprazole sodium form B as defined in any of claims 1-4 in admixture with a pharmaceutically acceptable excipient.

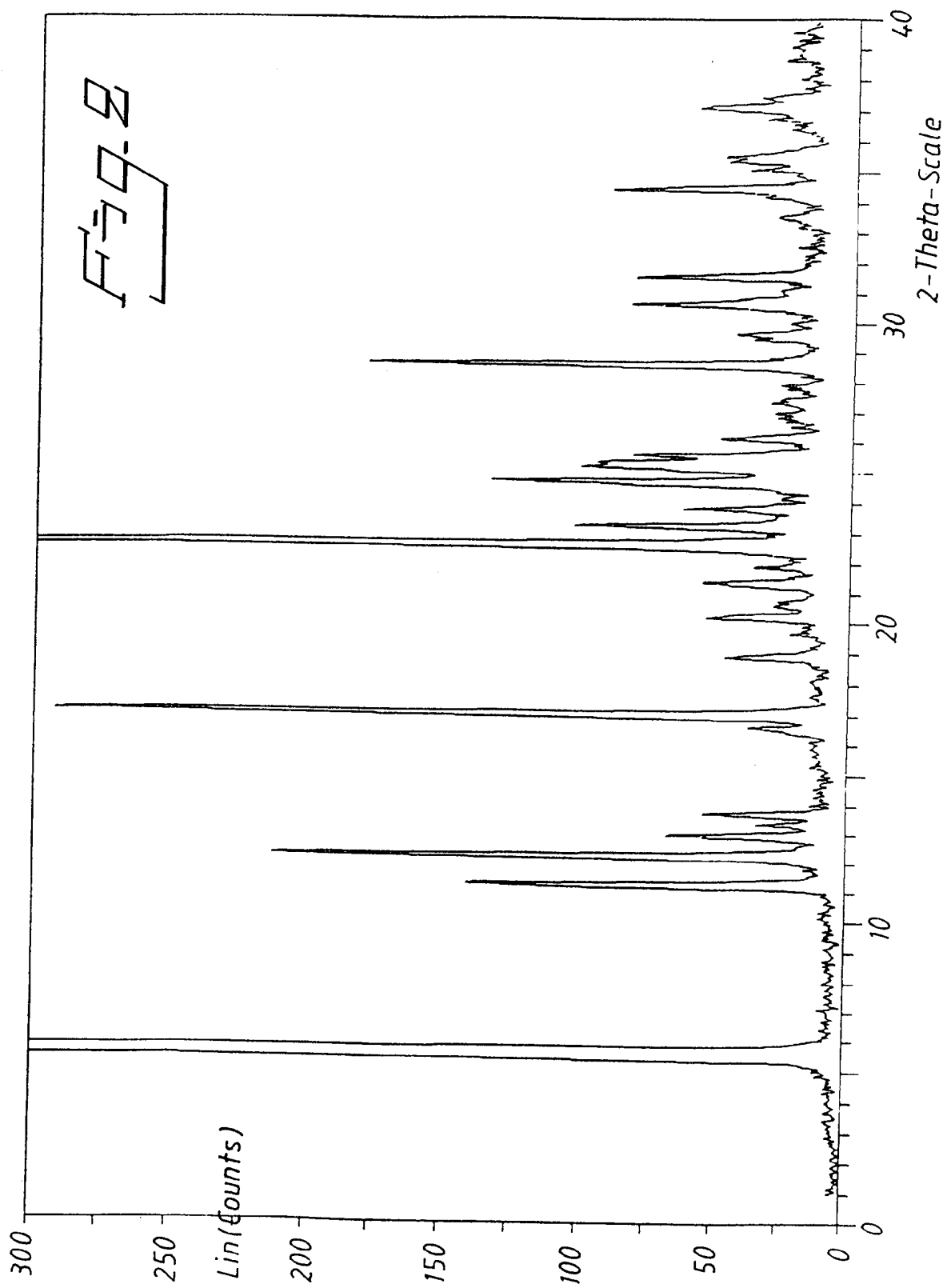
10. A pharmaceutical formulation suitable for i.v. administration comprising omeprazole sodium form B as defined in any of claims 1-4 in admixture with a pharmaceutically acceptable excipient.
- 5 11. The use of omeprazole sodium form B as defined in any of claims 1-4, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.
12. The use of omeprazole sodium form B as defined in any of claims 1-4 in the  
10 manufacture of a pharmaceutical formulation for i.v. administration.
- 13 A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of omeprazole sodium form B as defined in any of claims 1-4, to a patient suffering from gastrointestinal disorders.



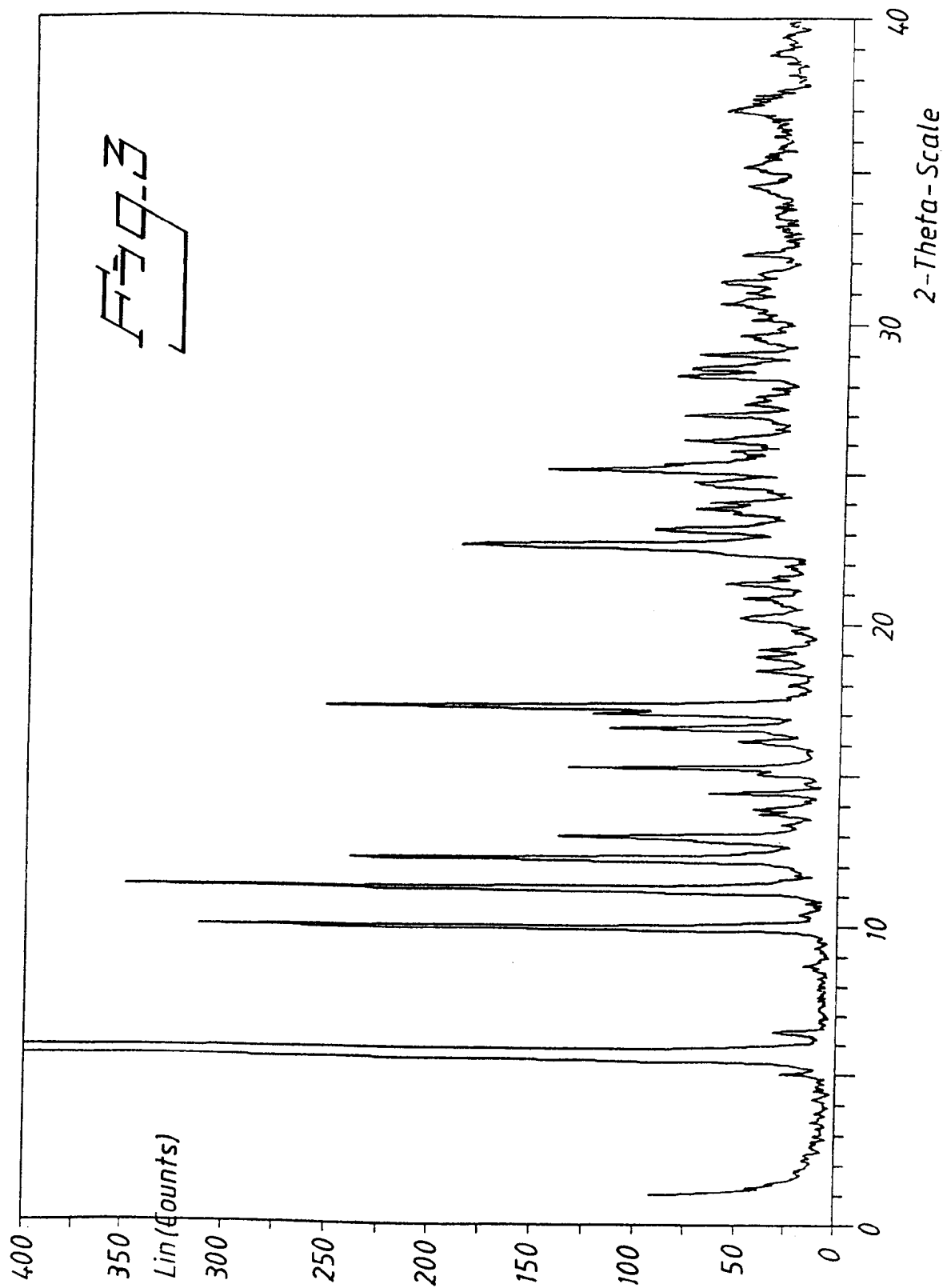
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2 / 3



3 / 3



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01124

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0124495 A2 (AKTIEBOLAGET HÄSSLE), 7 November 1984 (07.11.84)  -- -----	1-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

23 Sept 1998

Date of mailing of the international search report

12-10-1998

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/01124

**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13  
because they relate to subject matter not required to be searched by this Authority, namely:  
A method for treatment of the human or animal body by therapy,  
see rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.

PCT/SE 98/01124

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0124495 A2	07/11/84	SE 0124495 T3	
		AU 563842 B	23/07/87
		AU 2525784 A	06/09/84
		BG 44538 A	15/12/88
		BG 60837 B	30/04/96
		CA 1264751 A	23/01/90
		CS 241150 B	13/03/86
		CS 8401515 A	13/06/85
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<b>(54) Title:</b> NEW CRYSTALLINE FORM OF OMEPRAZOLE		
<b>(57) Abstract</b>		
<p>The present invention relates to a novel crystalline form of 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole, know under the generic name omeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-methoxy-2-[[ (4-methoxy-3,5-dimethyl- 2-pyridinyl)methyl] sulfinyl]-1H- benzimidazole.</p>		

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## NEW CRYSTALLINE FORM OF OMEPRAZOLE

*Field of the invention*

5 The present invention relates to a novel crystalline form of 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is known under the generic name omeprazole and its novel crystalline form is hereinafter referred to as omeprazole form A. Further, the present invention also relates to use of omeprazole form A for the treatment of  
10 gastrointestinal disorders, pharmaceutical compositions containing omeprazole form A and processes for the preparation of omeprazole form A.

*Background of the invention and prior art*

15 The compound 5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, as well as therapeutically acceptable salts thereof, are described in EP 5129. The single crystal X-ray data and the derived molecular structure of the so far only known crystal form of omeprazole is described by Ohishi *et al.*, Acta Cryst. (1989), C45, 1921-1923. This published crystal form of  
20 omeprazole is hereinafter referred to as omeprazole form B.

Omeprazole is a proton pump inhibitor, *i.e.* effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for treatment of gastric-acid related diseases in mammals and especially in man.

25

*Brief description of the drawings*

Figure 1 is an X-ray powder diffractogram of omeprazole form A.

Figure 2 is an X-ray powder diffractogram of omeprazole form B.

*Description of the invention*

It has surprisingly been found that the substance omeprazole can exist in more than one  
5 crystal form. It is an object of the present invention to provide omeprazole form A. Another  
object of the present invention is to provide a process for the preparation of omeprazole  
form A, substantially free from other forms of omeprazole. X-ray powder diffraction  
(XRPD) is used as a method of differentiating omeprazole form A from other crystalline  
and non-crystalline forms of omeprazole. Additionally it is an object of the present  
10 invention to provide pharmaceutical formulations comprising omeprazole form A.

Omeprazole form A is a crystalline form exhibiting advantageous properties, such as being  
well-defined, being thermodynamically more stable and less hygroscopic than omeprazole  
form B, especially at room temperature. Omeprazole form A does also show a better  
15 chemical stability, such as thermo stability and light stability, than omeprazole form B.

Omeprazole form B can under certain conditions, completely or partly, be converted into  
omeprazole form A. Omeprazole form A is thereby characterized in being thermo-  
dynamically more stable than omeprazole form B.

20

Omeprazole form A is further characterized as being essentially non-hygroscopic.

Omeprazole form A is characterized by the positions and intensities of the peaks in the X-  
ray powder diffractogram, as well as by the unit cell parameters. The unit cell dimensions  
25 have been calculated from accurate Guinier data. The X-ray powder diffractogram data as  
well as the unit cell parameters for omeprazole form B are different compared to  
omeprazole form A. Omeprazole form A can thereby be distinguished from omeprazole  
form B, using X-ray powder diffraction.

Omeprazole form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the Guinier diffractogram of omeprazole form A. The relative

intensities are less reliable and instead of numerical values the following definitions are used;

	% Relative Intensity*	Definition
5	25-100	vs (very strong)
	10-25	s (strong)
	3-10	m (medium)
	1-3	w (weak)

\* The relative intensities are derived from diffractograms measured with fixed slits.

10

Omeprazole form A according to the present invention is further characterized by a triclinic unit cell with parameters;

$$a=10.410(4) \text{ \AA}$$

$$b=10.468(3) \text{ \AA}$$

$$c=9.729(4) \text{ \AA}$$

$$\alpha=111.51(3)^\circ$$

$$\beta=116.78(3)^\circ$$

$$\gamma=90.77(3)^\circ$$

15 Omeprazole form A can also be characterized by Raman spectroscopy, where omeprazole form A is characterized by the absence of a band at  $1364 \text{ cm}^{-1}$ , which is observed for omeprazole form B, and by the ratio of the relative intensities of the  $842 \text{ cm}^{-1}$  and  $836 \text{ cm}^{-1}$  bands. The ratio (intensity of  $842 \text{ cm}^{-1}$  band / intensity of  $836 \text{ cm}^{-1}$  band) is  $<1$  for omeprazole form A, while the ratio is  $>1$  for omeprazole form B.

20

According to the invention there is further provided a process for the preparation of omeprazole form A.

Omeprazole form A is obtained upon slow crystallization and omeprazole form B is obtained from fast crystallization. Omeprazole form A may be prepared by reaction crystallisation or recrystallizing omeprazole of any form, or mixtures of any forms, in an appropriate solvent, such as for instance methanol, at around room temperature and for a  
5 prolonged time period. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks. Suitable solvents are alkyl alcohols and especially a lower alcohol comprising 1 - 4 carbon atoms.

Omeprazole form A may also be prepared by suspending omeprazole of any form, or  
10 mixtures of any forms, in an appropriate solvent at around room temperature and for a prolonged time period. Examples of appropriate solvents include, but are not limited to, methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene, or any mixture thereof. Examples of prolonged time periods include, but are not limited to, a few hours, such as 2 hours, up to several weeks.

15 The omeprazole form A obtained according to the present invention is substantially free from other crystal and non-crystal forms of omeprazole, such as omeprazole form B. Substantially free from other forms of omeprazole shall be understood to mean that omeprazole form A contains less than 10%, preferably less than 5%, of any other forms of  
20 omeprazole, *e.g.* omeprazole form B.

Omeprazole form A in mixture with other solid form/forms of omeprazole, *e.g.* omeprazole form B, also exhibits advantageous properties, such as being chemically more stable than pure omeprazole form B. Mixtures comprising a certain amount of omeprazole form A, by  
25 weight, are also chemically more stable than other mixtures comprising a lesser amount of omeprazole form A, by weight. Such mixtures comprising omeprazole form A can be prepared, for example, by mixing omeprazole form A prepared according to the present invention with other solid forms of omeprazole, such as form B, prepared according to prior art.

The present invention also relates to mixtures comprising omeprazole form A in mixture with other solid forms of omeprazole. Such mixtures comprising omeprazole form A include for instance mixtures containing a detectable amount of omeprazole form A, 1%, 2%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98% or 99% (by weight), of omeprazole form A.

Examples of other solid forms of omeprazole include, but are not limited to, omeprazole form B, amorphous forms, and other polymorphs.

A detectable amount of omeprazole form A is an amount that can be detected using conventional techniques, such as FT-IR, Raman spectroscopy, XRPD and the like.

The expression chemical stability includes, but is not limited to, thermo stability and light stability.

The compound of the invention, *i.e.* omeprazole form A, prepared according to the present invention is analyzed, characterized and differentiated from omeprazole form B by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate omeprazole form A from omeprazole form B is by Raman spectroscopy.

Omeprazole form A is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including *e.g.* reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable *e.g.* in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent

aspiration of gastric acid and to treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

5

Any suitable route of administration may be employed for providing the patient with an effective dosage of omeprazole form A according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like, *e.g.* enteric-coated capsules and/or tablets, capsules and/or tablets containing enteric-coated pellets of omeprazole. In all dosage forms omeprazole form A can be admixed with other suitable constituents. .

10

According to the invention there is further provided a pharmaceutical composition comprising omeprazole form A, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of *Helicobacter* infections. The invention also provides the use of omeprazole form A in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of omeprazole form A.

15

20

The compositions of the invention include compositions suitable for peroral or parenteral administration. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

25

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of omeprazole form A in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special

30

requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use  
5 doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

In general, a suitable oral dosage form may cover a dose range from 5 mg to 250 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage  
10 range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are  
15 hereby incorporated as a whole by reference.

Combination therapies comprising omeprazole form A and other active ingredients in separate dosage forms, or in one fixed dosage form, may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory  
20 agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, i.e. omeprazole form A, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

25

### *Examples*

#### Example 1



*Preparation of omeprazole form A*

Omeprazole (55.8 g) is added at room temperature to methanol (348 ml) containing ammonia (1.3 ml; 25%). The suspension is thereafter stirred in darkness for approximately  
5 45 hours and then filtered. The filtrate is dried 18 hours at 30°C under reduced pressure (<5 mbar). Yield: 43.9 g.

Example 210 *Preparation of omeprazole form B*

Omeprazole (50 g) is added to methanol (750 ml) containing ammonia (0.7 ml; 25%) at 50°C. The solution is thereafter filtered and cooled in about 20 minutes to approximately 0°C. The formed crystals are filtered and washed with ice cooled methanol and then dried.  
15 The filtrate was dried 24 hours at 40°C under reduced pressure (<5 mbar). Yield: 39 g.

Example 320 *Characterization of omeprazole form A and omeprazole form B using X-ray powder diffraction*

X-ray diffraction analysis was performed according to standard methods which can be found in *e.g.* Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H.P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and  
25 Sons, New York. The unit cell parameters for omeprazole form A and B have been calculated from the Guinier X-ray powder diffractograms using the program "TREOR" by Werner, P.-E., Eriksson, L. and Westdahl, M., J. Appl. Crystallogr. 18 (1985) 367 - 370. The fact that the positions of all peaks in the diffractograms for omeprazole form A and form B may be calculated using the respective unit cell parameters, proves that the unit cells are

correct and that the diffractograms are indicative of the pure forms. The diffractogram of omeprazole form A, prepared according to Example 1 in the present application, is shown in Figure 1 and the diffractogram of omeprazole form B, prepared according to Example 2 in the present application is shown in Figure 2.

5

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractograms for omeprazole forms A and form B, and are given in Table 1. In this table the unit cell parameters for omeprazole forms A and B are also given. The relative intensities are less reliable and instead of numerical values the

10 following definitions are used;

% Relative Intensity	Definition
25-100	vs (very strong)
10-25	s (strong)
15 3-10	m (medium)
1-3	w (weak)

Some additional weak or very weak peaks found in the diffractograms have been omitted from table 1.

20

Table 1. X-ray powder diffraction data for omeprazole form A and form B shown in Figures 1 and 2. All peaks noted for omeprazole form A and form B can be indexed with the unit cells given below.

Form A		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	9.6	vs
7.9	s	8.0	m
7.4	w	7.9	m
7.2	vs	7.5	w
6.0	m	7.1	vs
5.6	s	5.9	m
5.2	s	5.6	m
5.1	s	5.3	s
4.89	w	5.1	s
4.64	m	4.54	m
4.60	m	4.48	s
4.53	w	4.41	m
4.49	m	4.14	w
4.31	m	3.75	s
4.19	w	3.57	m
4.15	w	3.47	s
3.95	w	3.40	w
3.71	s	3.28	s
3.59	m	3.22	m
3.48	m	3.02	w
3.45	s	2.97	w

Form A		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
3.31	w	2.87	w
3.22	s	2.37	w
3.17	m		
3.11	w		
3.04	w		
3.00	w		
2.91	w		
2.86	w		
2.85	w		
2.75	w		
2.67	w		
2.45	w		
2.41	w		

The triclinic unit cells are:

Unit cell form A

$a=10.410(4)$  Å

$b=10.468(3)$  Å

$c=9.729(4)$  Å

$\alpha=111.51(3)^\circ$

$\beta=116.78(3)^\circ$

$\gamma=90.77(3)^\circ$

Unit cell form B

$a=10.257(10)$  Å

$b=10.717(6)$  Å

$c=9.694(10)$  Å

$\alpha=112.14(7)^\circ$

$\beta=115.56(5)^\circ$

$\gamma=91.76(7)^\circ$

*CLAIMS*

1. Omeprazole form A, characterized in being thermodynamically stable at room temperature.
2. Omeprazole form A, characterized in being essentially non-hygroscopic.
3. Omeprazole form A according to claims 1 or 2, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values;

<b>Form A</b>		<b>Form A</b>	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
9.5	vs	3.71	s
7.9	s	3.59	m
7.4	w	3.48	m
7.2	vs	3.45	s
6.0	m	3.31	w
5.6	s	3.22	s
5.2	s	3.17	m
5.1	s	3.11	w
4.89	w	3.04	w
4.64	m	3.00	w
4.60	m	2.91	w
4.53	w	2.86	w
4.49	m	2.85	w
4.31	m	2.75	w
4.19	w	2.67	w
4.15	w	2.45	w
3.95	w	2.41	w

4. Omeprazole form A, according to any of claims 1-3, characterized by having a triclinic unit cell with parameters

5      $a=10.410(4) \text{ \AA}$ ,  $b=10.468(3) \text{ \AA}$ ,  $c=9.729(4) \text{ \AA}$ ,  $\alpha=111.51(3)^\circ$ ,  $\beta=116.78(3)^\circ$ ,  
 $\gamma=90.77(3)^\circ$ .

5. Omeprazole, characterized in containing more than 50%, by weight, of omeprazole form A according to any of claims 1-4.

10

6. A process for the preparation of omeprazole form A as defined in any of claims 1-4, comprising the steps of;

a) dissolving or suspending omeprazole of any form, or a mixture of any form, in a suitable solvent;

15

b) allowing the solution to crystallize, optionally using omeprazole form A to induce crystallization, and

c) isolating the omeprazole form A thus obtained.

20

7. A process according to claim 6, characterized in that the solvent used in step a) is chosen from a group consisting of methanol, ethanol, acetone, ethyl acetate, methyl tert. butyl ether, toluene, or any mixture thereof.

25

8. A process according to claims 6 or 7, characterized in that step a) is performed at 15-25°C.
9. A process according to any of claims 6-8, characterized in that step b) is performed during a prolonged time period.

10. A process according to any claim 6-9, characterized in that step b) is performed during at least 2 hours.

11. Omeprazole form A, prepared by a process according to any of claims 6-10.

5

12. A pharmaceutical formulation comprising omeprazole as defined in any of claims 1-5 in admixture with a pharmaceutically acceptable excipient.

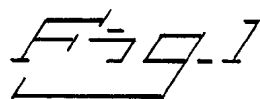
13. The use of omeprazole as defined in any of claims 1-5, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

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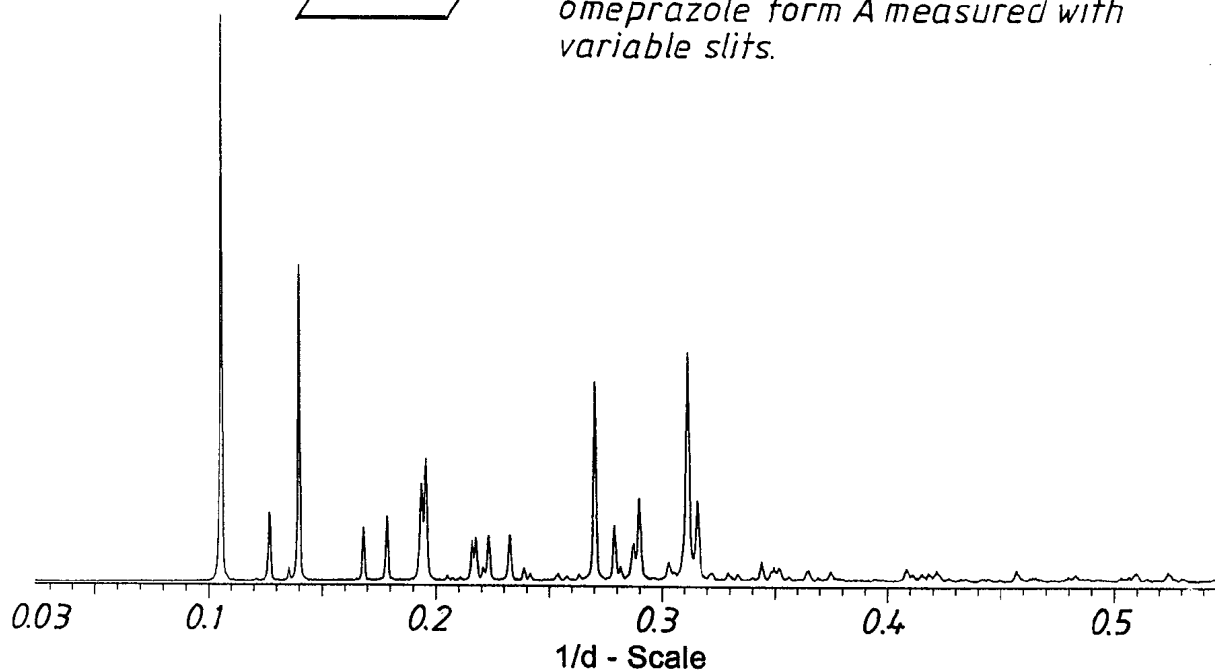
14. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of omeprazole as defined in any of claims 1-5, to a patient suffering from gastrointestinal disorders.

15

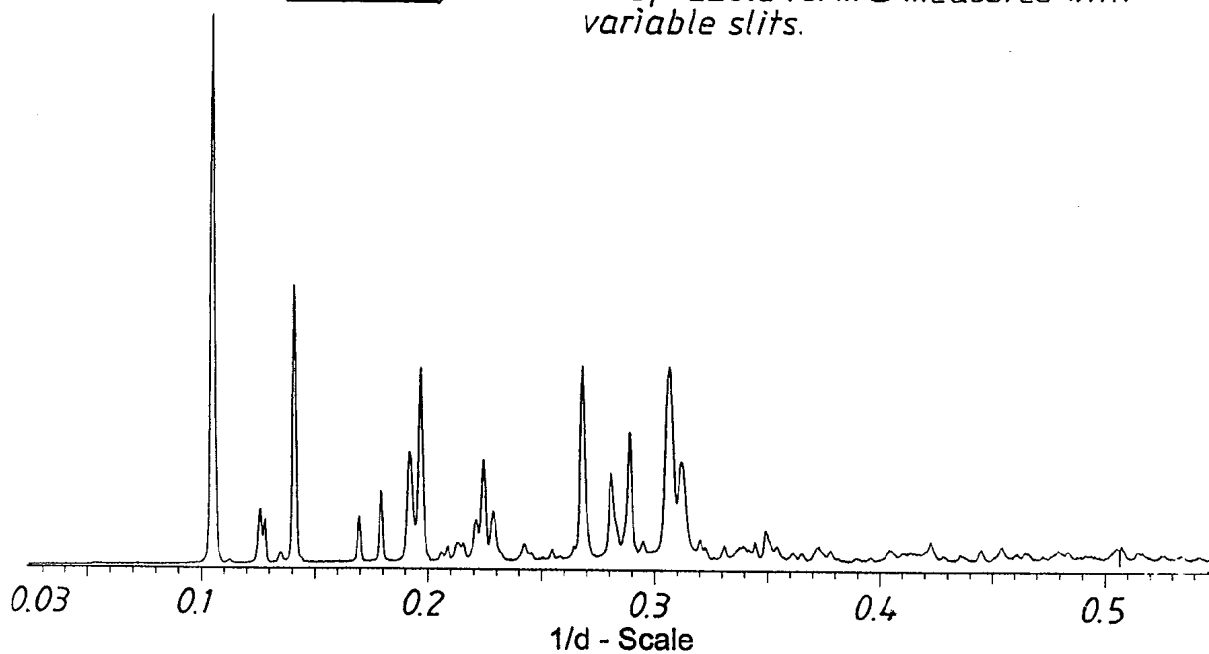
1 / 1



An X-ray powder diffractogram of omeprazole form A measured with variable slits.



An X-ray powder diffractogram of omeprazole form B measured with variable slits.







## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 9/28, 9/30, 9/32, 9/34, 9/36, 9/38, 9/42</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/25323</b> <b>(43) International Publication Date:</b> 27 May 1999 (27.05.99)
<b>(21) International Application Number:</b> PCT/US98/24195 <b>(22) International Filing Date:</b> 13 November 1998 (13.11.98) <b>(30) Priority Data:</b> 08/970,489 14 November 1997 (14.11.97) US <b>(71) Applicant:</b> ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US). <b>(72) Inventors:</b> CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). CHOU, Joseph, C.H.; 5755 N.W. 54th Place, Coral Springs, FL 33067 (US). WENG, Timothy; 3 South Pine Island, Plantation, FL 33324 (US). <b>(74) Agent:</b> COSTIGAN, James, V.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> OMEPRAZOLE FORMULATION  <b>(57) Abstract</b>  A pharmaceutical composition of omeprazole for oral administration is described which consists essentially of (a) a pellet comprising an inert core component, a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and (b) a single layer of coating on said pellet which comprises a layer of an enteric coating agent.		

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## OMEPRAZOLE FORMULATION

BACKGROUND OF THE INVENTION:

The present invention relates to a stable  
5 formulation of omeprazole. It is well known that  
omeprazole is sensitive to acidic conditions and the  
after contact with an acid, omeprazole will degrade and  
will not function in its intended manner. Initially,  
alkaline materials were added to a core of omeprazole  
10 and later an enteric coating was applied over the core  
to prevent the omeprazole from contacting the acidic pH  
conditions of the stomach. This approach is  
satisfactory if the product is administered within a  
short time after it is manufactured but if the product  
15 is stored under ambient conditions, the acidic residue  
of the enteric coating appears to degrade the  
omeprazole before it is administered to a patient. To  
solve this problem, the prior art has used a separate  
layer of a coating agent to coat a pellet core which  
20 contains omeprazole and an alkaline material which is  
thereafter coated with the enteric coating. This  
technique is described in U.S. 4,786,505.

This dual layer coating technique requires  
the application of two separate functional coating  
25 operations which increases the length of the  
manufacturing process and the cost of the product. The  
applicants have surprisingly discovered a coating  
system which avoids the need to use a coating layer to  
separate the omeprazole core from the enteric coating  
30 layer in an omeprazole dosage form. The separate  
coating system is based on the combined use of an  
enteric coating agent which is applied to pellet cores  
of omeprazole as a suspension in a suitable solvent.

SUMMARY OF THE INVENTION

The present invention provides a novel dosage form of omeprazole which consists essentially of:

- (a) a pellet comprising an inert core component, a therapeutically effective amount of omeprazole, a surface active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder; and  
(b) a single layer of coating on said pellet which comprises a layer of an enteric coating agent.

Accordingly, it is a primary object of this invention to provide a pharmaceutical dosage formulation of omeprazole which is stable upon prolonged storage, is stable when administered to a patient and is capable of providing the desired therapeutic effect.

It is also an object of this invention to provide a pharmaceutical dosage form of omeprazole which is bioequivalent to dosage forms of omeprazole which have an intermediate layer of an inert coating material.

It is also an object of this invention to provide a stable dosage form of omeprazole which may be produced without the need to provide an intermediate coating layer that separates the omeprazole containing core from the enteric coating layer.

These and other objects of the invention will become apparent from a review of the appended specification.

#### DETAILED DESCRIPTION OF THE INVENTION

The omeprazole formulation of the invention is preferably based on pellets having a core forming inert component which may comprise a starch or sugar sphere such as non-pareil sugar seeds having an average size of from 14 to 35 mesh, preferably about 18 to 20 mesh. The core forming inert component is coated with a formulation which comprises omeprazole, a surface active agent, a filler, an alkaline material and a binder,

which are collectively referred to hereafter as the drug layer composition. The core forming inert component is employed at 1:1 to 5:1 and preferably from 2:1 to 3:1 weight ratio to the drug layer composition.

5           The omeprazole may comprise from 20 to 70wt% and preferably 40 to 50wt% of the drug layer composition.

          The surface active agent may be any pharmaceutically acceptable, non-toxic surfactant.  
10   Suitable surface active agents include sodium lauryl sulfate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 and the like.

          The surface active agent may be present at a level of from 0.1 to 5wt% and preferably 0.25 to 2.5wt%  
15   based on the total weight of the drug layer composition.

          The alkaline material is selected from the group consisting of the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid and aluminum/magnesium  
20   compounds such as  $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$ ,  $(\text{Mg}_6\text{Al}_2(\text{OH}_{1-6}\text{CO}_3 \cdot 4\text{H}_2\text{O}))$ ,  $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$  where n is a whole integer of 2 or more. In addition the alkaline material may be selected from the group consisting of antacid materials such as aluminum hydroxides, calcium  
25   hydroxides, magnesium hydroxides and magnesium oxide. The alkaline agent may be present at a level of 1 to 20wt% based on the total weight of the coating composition, depending on the relative strength of the alkaline material. If the preferred disodium phosphate  
30   alkaline agent is employed, a level of from 1 to 10wt% and preferably 4 to 7wt% based on the weight of the drug layer composition may be employed.

          The binder may be any pharmaceutically acceptable, non-toxic pharmaceutically acceptable  
35   binder.

          The binder is preferably a water soluble polymer of the group consisting of polyvinyl alcohol,

polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and the like. A water soluble binder is preferred which is applied from an aqueous medium such as water at a level of from 0.1 to 5wt% and preferably from 0.25 to 3wt% of binder based on the total weight of the drug layer composition.

A filler is added to the drug layer. Sugars such as lactose, dextrose, sucrose, maltose, microcrystalline cellulose and the like may be used as fillers in the pellet coating composition. The filler may comprise from 20 to 70wt% and preferably 40 to 50wt% based on the total weight of the drug layer composition.

The enteric coating agent may comprise a acid resisting material which resists acid up to a pH of above about 5.0 or higher which is selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, Eudragit L (poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit S (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B) and mixtures thereof.

The enteric coating agent may also include an inert processing aid in an amount from 10 to 80wt % and preferably 30 to 50wt% based on the total weight of the acid resisting component and the inert processing aid. The inert processing aids include finely divided forms of talc, silicon dioxide, magnesium stearate etc. Typical solvents which may be used to apply the acid resisting component-inert processing aid mixture include isopropyl alcohol, acetone, methylene chloride and the like. Generally the acid resistant component-inert processing aid mixture will be applied from a 5 to 20wt% of acid resisting component-inert processing aid mixture based on the total weight of the solvent and the acid resistant component-inert processing aid.

The cores are formed by spraying the non-

pareil seeds with an aqueous or non-aqueous suspension which contains the alkaline agent, the omeprazole, the surface active agent and the binder. The suspension medium may comprise any low viscosity solvent such as water, isopropyl alcohol, acetone, ethanol or the like. When fluids such as water are employed, this will usually require a weight of fluid which is about seven times the weight of the dry components of the coating composition.

After the cores are dried, the cores are coated with the enteric coating agent. A color imparting agent may be added to the enteric coating agent mixture or a rapidly dissolving seal coat containing color may be coated over the enteric coating agent layer provided that the seal coat is compatible with and does not affect the dissolution of the enteric coating layer.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

##### EXAMPLE 1

Active pellets of omeprazole are formed by placing sugar spheres in a fluidized bed coater and spraying a suspension containing omeprazole onto the sugar spheres. The formulation for making the active pellets has the following composition:

povidone, USP (Plasdone K90)	4.5g
sodium lauryl sulfate, NF	10.6g
lactose anhydrous, NF	427.7g
disodium phosphate, NF	51.3g
omeprazole, USP (micronized)	427.7g
purified water, USP	3336.0g

The povidone, lactose anhydrous, disodium phosphate and the purified water are mixed with a mechanical mixer until the materials are dissolved. Then

the sodium lauryl sulfate is added to the mixture with gentle stirring to avoid the formation of excess foam until it dissolves completely. At that time the micronized omeprazole is added to the mixture and gentle stirring is continued until the micronized omeprazole is completely dispersed.

2500.0g of non-pareil sugar spheres (USPXII) (18/20 mesh) are placed in the fluidized bed coater and the suspension containing the omeprazole is coated at a product temperature of 35-45°C; an atomization pressure of 1.5 - 3.0 bar and a pump rate of 2-50ml/minute, starting with a slow rate of pumping to avoid agglomeration and increasing the rate of pumping consistent with the avoidance of the formation of agglomerates.

After coating is complete the pellets are dried at a temperature of 50°C until the loss on drying is less than 2.5wt%. The pellets are then screened through a #14 mesh screen and coated with the following enteric coating formulation:

hydroxypropylmethylcellulose phthalate, NF	258.1g
cetyl alcohol, NF	12.9g
talc, USP	129.0g
isopropyl alcohol, USP*	1663.0g
acetone, NF*	1663.0g

\*evaporates during processing

The hydroxypropylmethylcellulose phthalate and the cetyl alcohol are mixed with the isopropyl alcohol and the acetone with agitation until all of the materials are dissolved. The talc is dispersed with agitation in this solution. One kilogram of the active pellets are placed in a fluidized bed coater and all of the enteric coating mixture is applied using the coating conditions that were used to form the active pellets. The enteric coated pellets are then placed into No. "2",



hard gelatin capsules containing pellets which are equivalent to 20mg of omeprazole.

The capsules were evaluated for stability as follows:

5 Dissolution stability:

After acid treatment for 2 hours in 500ml of 0.1N HCl solution at 37°C, the test samples were tested according to the USP XXII dissolution test (type 1, basket) at 100rpm, at 37° in phosphate buffer medium, USP XXII, at  
10 pH 6.8 to determine the percent of the drug dissolved versus time. The following results were obtained:

	Time (min)	Percent Dissolved			
		<u>initial</u>	<u>40°C/75%RH/1mo</u>	<u>40°C/75%RH/2mo</u>	<u>40°C/75%RH/3mo</u>
15	10	87	76	95	93
	20	90	88	96	95
	30	90	86	95	94
	60	86	81	91	89
20					

Chemical and Acid Resistance Stability:

25 The acid resistance study was conducted by using the USP XXII dissolution test (type 1, basket), 100rpm, 37°C., in a aqueous solution of hydrochloric acid at pH 1.0. The following results were obtained:

30

		<u>initial</u>	<u>40°C/75%RH/1mo</u>	<u>40°C/75%RH/2mo</u>	<u>40°C/75%RH/3mo</u>
35	potency (% of LC)	101%	101%	100%	100%
	acid resistance (% of LC)	97%	100%	100%	99%
40					

A biostudy was carried out to compare the product of Example 1 with Prilosec brand of omeprazole (Ref. Mean) in humans. The following results were obtained in fasting humans:

	<u>Example 1</u>	<u>Mean</u>	<u>%CV</u>	<u>Ref. Mean</u>	<u>%CV</u>	<u>Geometric</u>	<u>90%Confid.Interv.</u>	
						<u>ratio</u>	<u>low.lim</u>	<u>upp. lim</u>
10	Cmax	134.50	61.46	133.46	60.11	0.964	72.47%	128.19%
	AUC 0~t	224.38	68.94	214.61	66.24	1.040	96.08%	112.63%
	AUC 0~8	230.87	65.78	220.54	64.76	1.052	97.42%	113.62%
15	Tmax	2.33	39.90	1.92	44.93	1.232		

All of the components which are used in the present invention are used in amounts which are effective for the intended purpose for which the component is employed.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

## Claims:

1. A stable pharmaceutical composition of omeprazole for  
5 oral administration which consists essentially of:  
(a) a pellet comprising an inert core component, a  
therapeutically effective amount of omeprazole, a  
surface active agent, a filler, a pharmaceutically  
acceptable alkaline agent and a binder; and  
10 (b) a single layer of coating on said pellet which  
comprises a layer of an enteric coating agent.
2. A pharmaceutical composition of omeprazole as defined  
in claim 1 wherein the alkaline material is selected  
15 from the group consisting of the sodium, potassium,  
calcium, magnesium and aluminum salts of phosphoric  
acid, carbonic acid and citric acid.
3. A pharmaceutical composition of omeprazole as defined  
20 in claim 1 wherein the alkaline material is selected  
from the group consisting of aluminum hydroxides,  
calcium hydroxides, magnesium hydroxides and magnesium  
oxide.
- 25 4. A pharmaceutical composition of omeprazole as defined  
in claim 1 wherein the acid resistant component is  
selected from the group consisting of cellulose acetate  
phthalate, hydroxypropylmethyl cellulose phthalate,  
p o l y v i n y l   a c e t a t e   p h t h a l a t e ,  
30 carboxymethylethylcellulose, co-polymerized methacrylic  
acid/methacrylic acid methyl esters.
5. A pharmaceutical composition of omeprazole as defined  
in claim 1 wherein the enteric coating agent also  
35 includes an inert processing aid.
6. A pharmaceutical composition of omeprazole as defined

in claim 1 wherein the enteric coating agent around the core includes from 10 to 80wt% of and inert processing aid.

5 7. A pharmaceutical composition of omeprazole as defined in claim 1 which includes a sodium lauryl sulfate as the surface active agent.

8. A pharmaceutical composition as defined in  
10 claim 1 wherein the core contains a non-pareil sugar seed.

9. A pelleted pharmaceutical dosage formulation which consists essentially of:

15 (a) a core comprising a non-pareil sugar seed coated with drug layer composition comprising omeprazole, a binder, an alkaline agent, a filler and a surface active agent; and

(b) an enteric coating agent around said core, said  
20 enteric coating comprising hydroxypropylmethyl cellulose phthalate and talc.

10. A pelleted pharmaceutical dosage formulation as defined in claim 9 wherein the alkaline agent is  
25 disodium phosphate.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/24195

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/28, 9/30, 9/32, 9/34, 9/36, 9/38, 9/42,  
US CL : 424/474, 475, 476, 477, 479, 480, 481, 482

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## B. FIELDS SEARCHED

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NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,753,265 A (BERGSTRAND et al.) 19 MAY 1998, col. 6, lines 35-53, lines 50-58, col. 7, lines 10-27, col. 10, line 60 and col. 8, lines 30-65.	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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<b>(51) Internationale Patentklassifikation <sup>6</sup> :</b> <b>A61K 9/32, 9/36</b>	<b>A1</b>	<b>(11) Internationale Veröffentlichungsnummer: WO 99/27917</b> <b>(43) Internationales Veröffentlichungsdatum:</b> 10. Juni 1999 (10.06.99)
<b>(21) Internationales Aktenzeichen:</b> PCT/EP98/07645 <b>(22) Internationales Anmeldedatum:</b> 26. November 1998 (26.11.98) <b>(30) Prioritätsdaten:</b> 197 52 842.2 28. November 1997 (28.11.97) DE <b>(71) Anmelder (für alle Bestimmungsstaaten ausser US):</b> BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE). <b>(72) Erfinder; und</b> <b>(75) Erfinder/Anmelder (nur für US):</b> DIETRICH, Rango [DE/DE]; Im Tiergarten 16, D-78465 Konstanz (DE). NEY, Hartmut [DE/DE]; Peter-Thumb-Strasse 46, D-78464 Konstanz (DE). <b>(74) Gemeinsamer Vertreter:</b> BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).		<b>(81) Bestimmungsstaaten:</b> AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Veröffentlicht</b> <i>Mit internationalem Recherchenbericht.</i>
<b>(54) Title:</b> MEDICAMENT PREPARATION IN THE FORM OF A TABLET OR PELLET FOR ACID-LABILE ACTIVE SUBSTANCES <b>(54) Bezeichnung:</b> ARZNEIMITTELZUBEREITUNG IN TABLETTEN- ODER PELLETFORM FÜR SÄURELABILE WIRKSTOFFE <b>(57) Abstract</b> <p>The invention relates to a peroral medicament preparation in the form of a pellet or a tablet for acid-labile pyridine-2-ylmethylsulfinyl-1H-benzimidazoles comprising an alkaline pellet or tablet core and a coating made of one or more film formers which can be utilized for gastric juice resistant coatings, whereby the coating which is in direct contact with the pellet or tablet core is comprised of a neutralized film former. The novel preparation is characterized in that it can be simply produced and exhibits a high stability.</p> <b>(57) Zusammenfassung</b> <p>Es wird eine perorale Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-ylmethylsulfinyl-1H-benzimidazole umfassend einen alkalischen Pellet- oder Tablettenkern und einen Überzug aus einem oder mehreren für magensaftresistente Überzüge verwendbaren Filmbildner(n) angegeben, wobei der in direktem Kontakt mit dem Pellet- oder Tablettenkern stehende Überzug aus neutralisiertem Filmbildner besteht. Die neue Zubereitung zeichnet sich durch eine vereinfachte Herstellbarkeit sowie durch eine hohe Stabilität aus.</p>		

### **LEDIGLICH ZUR INFORMATION**

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<b>BY</b>	Belarus	<b>IS</b>	Island	<b>MX</b>	Mexiko	<b>US</b>	Vereinigte Staaten von Amerika
<b>CA</b>	Kanada	<b>IT</b>	Italien	<b>NE</b>	Niger	<b>UZ</b>	Usbekistan
<b>CF</b>	Zentralafrikanische Republik	<b>JP</b>	Japan	<b>NL</b>	Niederlande	<b>VN</b>	Vietnam
<b>CG</b>	Kongo	<b>KE</b>	Kenia	<b>NO</b>	Norwegen	<b>YU</b>	Jugoslawien
<b>CH</b>	Schweiz	<b>KG</b>	Kirgisistan	<b>NZ</b>	Neuseeland	<b>ZW</b>	Zimbabwe
<b>CI</b>	Côte d'Ivoire	<b>KP</b>	Demokratische Volksrepublik Korea	<b>PL</b>	Polen		
<b>CM</b>	Kamerun	<b>KR</b>	Republik Korea	<b>PT</b>	Portugal		
<b>CN</b>	China	<b>KZ</b>	Kasachstan	<b>RO</b>	Rumänien		
<b>CU</b>	Kuba	<b>LC</b>	St. Lucia	<b>RU</b>	Russische Föderation		
<b>CZ</b>	Tschechische Republik	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DE</b>	Deutschland	<b>LK</b>	Sri Lanka	<b>SE</b>	Schweden		
<b>DK</b>	Dänemark	<b>LR</b>	Liberia	<b>SG</b>	Singapur		
<b>EE</b>	Estland						

**Arzneimittelzubereitung in Tabletten- oder Pelletform für säurelabile Wirkstoffe**Gegenstand der Erfindung

Die vorliegende Erfindung bezieht sich auf eine perorale Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-yl-methylsulfinyl-1H-benzimidazole sowie Verfahren zur Herstellung dieser peroralen Arzneimittelzubereitungen.

Stand der Technik

Pyridin-2-yl-methylsulfinyl-1H-benzimidazole, wie sie beispielsweise aus EP-A-0005129, EP-A-0166287, EP-A-0174726 und EP-A-0268956 bekannt sind, besitzen aufgrund ihrer  $H^+/K^+$ -ATPase hemmenden Wirkung in erheblichem Maße Bedeutung bei der Therapie von Krankheiten, die von einer erhöhten Magensäuresekretion herrühren. Beispiele für im Handel befindliche Wirkstoffe aus dieser Gruppe sind 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazol (INN: Omeprazol), 5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazol (INN: Pantoprazol), 2-[3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]-methylsulfinyl]-1H-benzimidazol (INN: Lansoprazol) und 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazol (INN: Rabeprazol).

Wegen ihrer starken Neigung zur Zersetzung in neutraler und insbesondere saurer Umgebung, wobei auch stark gefärbte Zersetzungsprodukte entstehen, ist es für orale Zubereitungen erforderlich, die Wirkstoffe zum einen in alkalischer Umgebung zu halten und zum anderen vor der Einwirkung von Säuren zu schützen. Es ist allgemein bekannt, Tabletten oder Pellets, die einen säurelabilen Wirkstoff enthalten, mit einem magensaftresistenten Überzug zu beschichten, der sich nach der Magenpassage im alkalischen Milieu des Darms rasch auflöst. Bei den stark säurelabilen Pyridin-2-ylmethylsulfinyl-1H-benzimidazolen hat es sich als besonders zweckmäßig erwiesen, diese im Tablettenkern oder in Pellets in Form ihrer alkalischen Salze, beispielsweise als Natrium- oder Magnesiumsalze, und/oder zusammen mit alkalischen Substanzen zu verarbeiten.

Da es sich bei den für magensaftresistente Überzüge in Frage kommenden Stoffen um solche mit freien Carboxylgruppen handelt, ergibt sich das Problem, daß der magensaftresistente Überzug wegen des alkalischen Milieus im Innern von innen heraus an- oder gar aufgelöst wird und die freien Carboxylgruppen die Zersetzung der Wirkstoffe fördern. Es ist daher erforderlich, zwischen dem magensaftresistenten Überzug und dem alkalischen Tablettenkern oder Pellet eine isolierende Zwischenschicht (subcoating) vorzusehen.

In der EP-A-0244380 wird vorgeschlagen, Kerne, die den Wirkstoff zusammen mit alkalischen Verbindungen oder als alkalisches Salz enthalten, mit mindestens einer in Wasser löslichen oder in Was-



ser rasch zerfallenden Schicht aus nicht sauren, inerten pharmazeutisch annehmbaren Substanzen zu beschichten, bevor die magensaftresistente Schicht aufgebracht wird. Die Zwischenschicht bzw. Zwischenschichten wirken als pH-puffernde Zonen, in der die von außen hineindiffundierenden Wasserstoffionen mit den aus dem alkalischen Kern diffundierenden Hydroxylionen reagieren können. Um die Pufferkapazität der Zwischenschicht zu erhöhen, wird vorgeschlagen, Puffersubstanzen in die Zwischenschicht(en) einzuarbeiten. In der Praxis ist es nach diesem Verfahren möglich, einigermaßen stabile Zubereitungen zu erhalten. Jedoch benötigt man relativ dicke Zwischenschichten um die bereits bei einer nur geringfügigen Zersetzung auftretenden unansehnlichen Verfärbungen zu vermeiden. Außerdem ist bei der Herstellung ein erheblicher Aufwand zur Vermeidung von Feuchtigkeitsspuren zu treiben.

In der EP-A-0519365 wird für den Wirkstoff Pantoprazol eine Formulierung nach dem Prinzip des mit einer wasserlöslichen Zwischenschicht und einer magensaftresistenten Schicht überzogenen alkalischen Kerns vorgeschlagen, bei dem eine verbesserte Stabilität durch Verwendung von Polyvinylpyrrolidon und/oder Hydroxypropylmethylcellulose als Bindemittel für den alkalischen Kern erreicht wird.

Aus der EP-A-0342522 ist eine Formulierung für säureempfindliche Benzimidazole bekannt, bei der sich zwischen dem alkalischen Kern und dem magensaftresistenten Überzug eine Zwischenschicht befindet, die aus einem nur wenig wasserlöslichen filmbildenden Material, wie Ethylcellulose und Polyvinylacetat, und einem darin suspendierten wenig wasserlöslichen feinkörnigen anorganischen oder organischen Material, wie beispielsweise Magnesiumoxid, Siliziumoxid oder Sucrosefettsäureestern, zusammengesetzt ist.

Aus der JP-A-59020219 ist eine magensaftresistente Zubereitung für säurelabile Wirkstoffe bekannt, die unter dem magensaftresistenten Überzug eine Zwischenschicht aus einem filmbildenden Material, wie Hydroxypropylmethylcellulose, Hydroxypropylcellulose und Hydroxypropylmethylcellulosephthalat mit einem Gehalt an höheren Fettsäuren vorsieht.

In der DE-A-3233764 wird für magensaftresistente Zubereitungen eine Zwischenschicht vorgeschlagen, die aus einem wasserlöslichen Celluloseether und einer wasserlöslichen ein- oder mehrbasigen organischen Säure, wie beispielsweise Zitronensäure, Weinsäure und dergleichen, gebildet wird.

Im US-Patent 4,017,647 wird die Herstellung magensaftresistenter Überzüge nach folgendem Verfahren beschrieben: Die feste Arzneiform wird zunächst mit einer wässrigen Lösung einer filmbildenden Polymersubstanz mit Carboxylgruppen, die durch Salzbildung neutralisiert sind, überzogen. Die fertig überzogene feste Arzneiform wird dann in Kontakt mit einer starken anorganischen Säure gebracht, woraufhin in der äußeren Schicht des Überzugs freie Carboxylgruppen gebildet werden, die für die gewünschte Magensaftresistenz sorgen.

Aufgabe der vorliegenden Erfindung ist es, eine perorale Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-ylmethylsulfinyl-1H-benzimidazole zur Verfügung zu stellen, die sich durch eine hohe Resistenz gegen durch Feuchtigkeit und sonstige Einflüsse verursachte Zersetzung und Verfärbung des Wirkstoffs auszeichnet. Eine weitere Aufgabe ist darin zu sehen, mit möglichst wenig Hilfsstoffen auszukommen bei gleichzeitiger Verkürzung der Prozeßzeiten.

Es wurde nun überraschenderweise festgestellt, daß diese Aufgaben gelöst werden durch alleinige Verwendung eines für magensaftresistente Überzüge verwendbaren Filmbildners in teils neutralisierter Form.

#### Beschreibung der Erfindung

Gegenstand der Erfindung ist daher eine perorale Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-ylmethylsulfinyl-1H-benzimidazole, bestehend aus einem alkalischen Pellet- oder Tablettenkern, enthaltend den Wirkstoff in Form seines alkalischen Salzes und/oder unter Zusatz von alkalischen Stoffen, und einem Überzug aus einem oder mehreren für magensaftresistente Überzüge verwendbaren Filmbildner(n), wobei die Arzneimittelzubereitung dadurch gekennzeichnet ist, daß der in direktem Kontakt mit dem Kern stehende Überzug aus neutralisiertem Filmbildner besteht.

Weitere Gegenstände ergeben sich aus den Unteransprüchen.

Ein besonders bevorzugter Gegenstand sind erfindungsgemäße perorale Arzneimittelzubereitungen, die als säurelabiles Pyridin-2-ylmethylsulfinyl-1H-benzimidazol Omeprazol, Pantoprazol und/oder deren Salze enthalten.

Die erfindungsgemäßen peroralen Arzneimittelzubereitungen zeichnen sich gegenüber dem Stand der Technik durch eine überraschend hohe Stabilität aus. Von besonderem Vorteil ist, daß für die Herstellung des magensaftresistenten Überzugs mit einem einzigen Überzugsmaterial gearbeitet werden kann. Da das magensaftresistente Filmmaterial sowohl in der neutralisierten als auch in der ursprünglichen Form aus wäßriger Lösung bzw. wäßriger Dispersion aufgebracht werden kann, erübrigt sich der Einsatz organischer Lösungsmittel.

Für eine alkalische Reaktion des Pellet- oder Tablettenkerns wird diesem - sofern die gewünschte Erhöhung des pH-Wertes nicht bereits durch Verwendung des Wirkstoff-Salzes erzielt wird - eine anorganische Base beigemischt. Hier seien beispielsweise die pharmakologisch verträglichen Alkali-, Erdalkali- oder Erdmetallsalze schwacher Säuren sowie die pharmakologisch verträglichen Hydroxide und Oxide von Erdalkali- und Erdmetallen genannt. Als beispielhafte hervorzuhebende Base sei Natriumcarbonat genannt. Als alkalische Wirkstoffsalze seien beispielhaft Lithium-, Natrium-, Kalium-, Magnesium-, Calcium-, Titan-, Ammonium- oder Guanidiniumsalze genannt. Besonders erwähnenswert sind das Pantoprazol-Natriumsalz und das Omeprazol-Magnesiumsalz.

Neben Füllstoff und Bindemittel kommen bei der Tablettenkernherstellung noch weitere Hilfsstoffe, insbesondere Gleit- und Trennmittel sowie Tabletten-Sprengmittel zum Einsatz. Als Bindemittel kommt insbesondere Polyvinylpyrrolidon in verschiedenen Polymerisationsgraden in Frage. Als Gleit- und Trennmittel seien beispielsweise höhere Fettsäuren und deren Alkali- und Erdalkalisalze, wie z.B. Calciumstearat genannt. Als Tabletten-Sprengmittel kommen insbesondere chemisch indifferente Mittel infrage. Als bevorzugtes Tabletten-Sprengmittel seien (quer)vernetztes Polyvinylpyrrolidon, quervernetzte Natrium-Carboxymethylcellulosen und Natrium-Stärkeglykolat genannt.

Bezüglich bevorzugter Füllstoffe, Bindemittel und gegebenenfalls weiterer Hilfsstoffe wird auf die Ausführungen im europäischen Patent 589981 verwiesen.

Bezüglich der auf den Pellet- bzw. Tablettenkern aufzubringenden magensaftresistenten Überzugsmaterialien seien als verwendbare Filmpolymere beispielsweise Methacrylsäure/Methacrylsäuremethylester-Copolymerisat bzw. Methacrylsäure/Methacrylsäureethylester-Copolymerisat (Eudragit® L) oder Cellulose-Derivate wie Carboxymethylethylcellulose (CMEC, Duodcel), Celluloseacetatphthalat (CAP), Celluloseacetattrimellitat (CAT), Hydroxypropylmethylcellulosephthalat (HP50, HP55), Hydroxypropylmethylcelluloseacetatsuccinat (HPMCAS) oder Polyvinylacetatphthalat genannt, denen gewünschtenfalls noch Weichmacher (wie etwa Propylenglykol) und/oder weitere Zusatz- und Hilfsstoffe (z.B. Pigmente) beigefügt werden können.

Welche magensaftresistenten Überzugsmittel prinzipiell verwendet werden können, ist dem Fachmann aufgrund seines Fachwissens bekannt. Beispielsweise sei auf die Ausführungen in den europäischen Patenten 244380 und 589981 verwiesen. Vorteilhafterweise werden wässrige Lösungen (für den neutralisierten Anteil) bzw. Dispersionen geeigneter magensaftresistenter Polymere, wie beispielsweise ein Methacrylsäure/Methacrylsäuremethylester-Copolymerisat bzw. Methacrylsäure/Methacrylsäureethylester-Copolymerisat, gewünschtenfalls unter Zusatz geeigneter Weichmacher (z.B. Triethylcitrat) und/oder weiterer Zusatz- und Hilfsstoffe wie Glycerolester verwendet. Vorzugsweise wird als Glycerolester Glycerolmonostearat zugesetzt, das die Wasserdampfdurchlässigkeit der wässrig aufgetragenen Schicht reduziert, ohne die Auflösungsgeschwindigkeit im Dünndarm zu beeinträchtigen.

Das Auftragen des Überzugsmaterials erfolgt auf übliche Weise mit den für diese Zwecke geläufigen Apparaturen. Das mit dem Tabletten- bzw. Pelletkern direkt in Kontakt stehende magensaftresistente Filmmaterial wird erfindungsgemäß in neutralisierter Form aufgebracht. Hierfür wird die benötigte Menge Filmbildner, die vorzugsweise als wässrige Dispersion vorliegt, mit einer Base behandelt die in der Lage ist, die freien Carboxylgruppen des Filmbildners zu neutralisieren. Als geeignete Basen seien genannt Alkalicarbonate, wie z.B. Kaliumcarbonat, oder Alkalihydroxide, wie z.B. Natriumhydroxid, Ammoniumhydroxid oder Amine, wie beispielsweise Triethanolamin.

Die wäßrige Lösung des magensaftresistenten polymeren Filmbildners mit den neutralisierten Carboxylgruppen (die auch durch Auflösung der entsprechenden, in fester Form vorliegenden Salze hergestellt werden kann) zeigt üblicherweise einen pH-Wert von 4 bis 8, jedoch sind auch höhere pH-Werte, die auf einen Überschuß an Base zurückzuführen sind, nicht von Nachteil, da der Tabletten- bzw. Pelletkern ohnehin basisch reagiert.

Diese Lösung wird nun in üblicher Weise in einem dafür geeigneten Gerät auf die Pellet- bzw. Tablettenkerne aufgesprüht, bis eine ausreichende Schichtdicke erreicht ist. Anschließend wird eine Dispersion des magensaftresistenten polymeren Filmbildners in üblicher Weise aufgesprüht, bis eine ausreichende Schichtdicke erreicht ist. Hierzu wird vorteilhafterweise der gleiche Filmbildner verwendet, wie er in neutralisierter Form eingesetzt wurde. Es kann aber auch jedes beliebige andere magensaftresistente Überzugsmaterial verarbeitet werden.

In einer Ausgestaltung der Erfindung erfolgt der Übergang von neutralisiertem zu unbehandeltem magensaftresistenten Filmmaterial kontinuierlich. Hierzu wird das im Behälter der Dragiervorrichtung vorgelegte, mittels Pumpe in den Drapierkessel beförderte und dort versprühte filmbildende Material in seiner Zusammensetzung kontinuierlich von "neutralisiert" nach "nicht neutralisiert" geändert. Dies kann durch kontinuierliche Zugabe von nicht neutralisiertem Filmmaterial zu dem im Behälter vorliegenden neutralisierten Filmmaterial geschehen. Hierzu wartet man zunächst mit der Zugabe von nicht neutralisiertem Filmmaterial so lange, bis die Pellet- bzw. Tablettenkerne sicher mit einer durchgehenden Schicht an neutralisiertem Filmmaterial überzogen sind. Andererseits ist am Ende der Zugabe von nicht neutralisiertem Filmmaterial sicherzustellen, daß kein oder nur noch eine geringe Menge an neutralisiertem Filmmaterial im Behälter vorliegt. Technisch wird die optimale Zuführung des jeweils gewünschten Filmmaterials am besten so gelöst, daß die beiden Filmmaterialien in zwei getrennten, über ein T-Stück mit der Pumpe verbundenen Behältern vorgelegt werden, und daß anfangs ausschließlich neutralisiertes und am Ende ausschließlich nicht neutralisiertes Filmmaterial aufgesprüht wird.

Beispiele

Die folgenden Formulierungsbeispiele erläutern die Erfindung näher, ohne sie einzuschränken.

**Beispiel 1****Tabletten:**I. Herstellung des unüberzogenen K e r n s:

a) Pantoprazol-Na x 1,5 H <sub>2</sub> O	45,1 mg
b) Natriumcarbonat	10,0 mg
c) Mannitol	42,7 mg
d) Polyvidon, unlöslich	50,0 mg
e) Polyvidon K90	4,0 mg
f) Calciumstearat	3,2 mg
	<hr/>
	155,0 mg

a) wird mit einem Teil von b), c) und d) vermischt. Der Rest von b) und c) wird in die klare wäßrige Lösung von e) gegeben und mit b) auf einen pH-Wert >10 eingestellt. Mit dieser Lösung wird in der Wirbelschicht granuliert. Dem getrockneten Granulat wird der Rest von d) sowie f) zugesetzt und das Granulat auf einer geeigneten Tablettenmaschine verpreßt.

II. Schicht mit neutralisiertem magensaftresistenten Filmmaterial:

g) Eudragit® L 30 D	9,84 mg
h) Triethylcitrat	0,29 mg
i) Natriumcarbonat	0,78 mg
	<hr/>
	10,91 mg

Gesamtgewicht pro beschichtetem Kern 165,91 mg

i) wird in 22 mg Wasser gelöst, dann wird g) und nach dessen Auflösung h) zugegeben.

Die unter I. erhaltenen Tablettenkerne werden in einem geeigneten Gerät mit der oben erhaltenen Lösung in der errechneten Schichtdicke überzogen.

III. Magensaftresistenter Überzug:

k) Eudragit® L 30 D	13,64 mg
l) Triethylcitrat	1,36 mg
	<hr/>
	15,00 mg

Gesamtgewicht  
pro magensaftresistenter Filmtablette 180,91 mg

k) wird mit Wasser verdünnt und l) zugesetzt. Die Dispersion wird vor der Verarbeitung gesiebt.

Auf die unter II. erhaltenen beschichteten Kerne wird III. in geeigneten Apparaturen aufgesprüht.

## Beispiel 2

### Tabletten:

#### I. Herstellung des unüberzogenen Kerns:

a) Lansoprazol	30,0 mg
b) Natriumcarbonat	7,5 mg
c) Mannitol	32,0 mg
d) Polyvidon, unlöslich	37,5 mg
e) Polyvidon K90	3,0 mg
f) Calciumstearat	2,4 mg
	<hr/>
	112,4 mg

Die Herstellung der Kerne erfolgt analog Beispiel 1 Punkt I.

#### II. Schicht mit neutralisiertem magensaftresistenten Filmmaterial:

g) Eudragit® L 30 D	9,84 mg
h) Triethylcitrat	0,29 mg
i) Natriumcarbonat	0,78 mg
	<hr/>
	10,91 mg

Gesamtgewicht pro beschichtetem Kern 123,31 mg

i) wird in 22 mg Wasser gelöst, dann wird g) und nach dessen Auflösung h) zugegeben.

Die unter I. erhaltenen Tablettenkerne werden in einem geeigneten Gerät mit der oben erhaltenen Lösung in der errechneten Schichtdicke überzogen.

#### III. Magensaftresistenter Überzug:

k) Eudragit® L 30 D	13,64 mg
l) Triethylcitrat	1,36 mg
	<hr/>
	15,00 mg

Gesamtgewicht pro magensaftresistenter Filmtablette	138,31 mg
--	-----------

k) wird mit Wasser verdünnt und l) zugesetzt. Die Dispersion wird vor der Verarbeitung gesiebt.

Auf die unter II. erhaltenen beschichteten Kerne wird III. in geeigneten Apparaturen aufgesprüht.

### Beispiel 3

#### Tabletten:

##### I. Herstellung des unüberzogenen K e r n s:

a) Omeprazol-Na	42,6 mg
b) Natriumcarbonat	10,0 mg
c) Mannitol	42,7 mg
d) Polyvidon, unlöslich	50,0 mg
e) Polyvidon K90	4,0 mg
f) Calciumstearat	3,2 mg
	<hr/>
	152,5 mg

Die Herstellung der Kerne erfolgt analog Beispiel 1 Punkt I.

##### II. Schicht mit neutralisiertem magensaftresistenten Filmmaterial:

g) Eudragit® L 30 D	9,84 mg
h) Triethylcitrat	0,29 mg
i) Natriumcarbonat	0,78 mg
	<hr/>
	10,91 mg

Gesamtgewicht pro beschichtetem Kern	163,41 mg
--------------------------------------	-----------

i) wird in 22 mg Wasser gelöst, dann wird g) und nach dessen Auflösung h) zugegeben.

Die unter I. erhaltenen Tablettenkerne werden in einem geeigneten Gerät mit der oben erhaltenen Lösung in der errechneten Schichtdicke überzogen.

##### III. Magensaftresistenter Überzug:

k) Eudragit® L 30 D	13,64 mg
l) Triethylcitrat	1,36 mg
	<hr/>
	15,00 mg

Gesamtgewicht

pro magensaftresistenter Filmtablette 178,41 mg

k) wird mit Wasser verdünnt und l) zugesetzt. Die Dispersion wird vor der Verarbeitung gesiebt.

Auf die unter II. erhaltenen vorisolierten Kerne wird III. in geeigneten Apparaturen aufgesprüht.

#### Beispiel 4

##### Tabletten:

##### I. Herstellung des unüberzogenen Kernes:

Die Herstellung der Kerne erfolgt nach Beispiel 3 Punkt I.

##### II. Lösung mit dem neutralisierten magensaftresistenten Filmmaterial:

g) Eudragit® L 30 D	9,15 mg
h) Triethylcitrat	0,91 mg
i) Natriumhydroxid	0,73 mg
	<hr/>
	10,79 mg

##### III. Dispersion mit dem magensaftresistenten Filmmaterial:

k) Eudragit® L 30 D	13,64 mg
l) Triethylcitrat	1,36 mg
	<hr/>
	15,00 mg

Die Bestandteile für die Lösung II werden in Wasser (20,5 mg) gelöst und in Behälter A gefüllt. Die Bestandteile für Dispersion III werden in Wasser (30 mg) dispergiert und in Behälter B gefüllt. Behälter A und B sind untereinander über ein T-Stück mit der Schlauchpumpe verbunden, die die Druckluft-Sprühdüse des Dragierkessels versorgt. Die Zuleitungen der Behälter A und B zum T-Stück sind jeweils mit einem Absperrhahn versehen.

Die Beschichtung der Tabletten im Dragierkessel mittels Besprühung wird so vorgenommen, daß zunächst nur Flüssigkeit aus Behälter A der Schlauchpumpe zugeführt wird. Dann wird in wachsendem Anteil Flüssigkeit auch aus Behälter B zugeführt. Für die letzten 40 % an Schichtdicke wird Flüssigkeit ausschließlich aus Behälter B zugeführt.

Die Beschichtung wird so lange durchgeführt, bis ein Gewichtszuwachs von ca. 25 mg/Tbl. erreicht ist.



**Beispiel 5****Pellets:**I. Starterpellets

- |    |   |         |
|----|---|---------|
| a) | Saccharose Pellets (0,7-0,85 mm)        | 950,0 g |
| b) | Hydroxypropylmethylcellulose 2910 (USP) | 50,0 g  |

a) wird mit der wäßrigen Lösung von b) in der Wirbelschicht (Wurster-Verfahren) besprüht.

II. Aktivpellets

- |    |   |         |
|----|---|---------|
| c) | Lansoprazol                             | 403,0 g |
| d) | Hydroxypropylmethylcellulose 2910 (USP) | 40,3 g  |

c) und d) werden nacheinander in 30% Isopropanol gelöst und auf 900 g der unter I. erhaltenen Pellets I. in der Wirbelschicht (Wurster-Verfahren) aufgesprüht.

III. Mit neutralisiertem magensaftresistenten Filmmaterial überzogene Pellets

Der Überzug erfolgt analog zu der bei Tabletten beschriebenen Vorgehensweise im Kessel oder in der Wirbelschicht.

IV. Magensaftresistent überzogene Pellets

Der Überzug erfolgt analog zu der bei Tabletten beschriebenen Vorgehensweise im Kessel oder in der Wirbelschicht.

Anschließend werden die Pellets in Kapseln geeigneter Größe (z.B. 1) abgefüllt.

Patentansprüche

1. Perorale Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-ylmethylsulfinyl-1H-benzimidazole, bestehend aus einem alkalischen Pellet- oder Tablettenkern, enthaltend den Wirkstoff in Form seines alkalischen Salzes und/oder unter Zusatz von alkalischen Stoffen, und einem Überzug aus einem oder mehreren für magensaftresistente Überzüge verwendbaren Filmbildner(n), dadurch gekennzeichnet, daß der in direktem Kontakt mit dem Pellet- oder Tablettenkern stehende Überzug aus neutralisiertem Filmbildner besteht.
2. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß als Filmbildner Methacrylsäure/Methacrylsäuremethylester-Copolymerisate, Methacrylsäure/Methacrylsäureethylester-Copolymerisate, Cellulose-Derivate und/oder Polyvinylacetatphthalate verwendet werden.
3. Perorale Arzneimittelzubereitung nach Anspruch 2, dadurch gekennzeichnet, daß als Cellulose-derivate Carboxymethylethylcellulose, Celluloseacetatphthalat, Celluloseacetattrimellitat, Hydroxypropylmethylcellulosephthalat und/oder Hydroxypropylmethylcelluloseacetatsuccinat verwendet werden.
4. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der neutralisierte Filmbildner durch Umsetzung des Filmbildners mit einer oder mehreren Basen hergestellt wird, die ausgewählt sind aus der Gruppe bestehend aus Alkalicarbonaten, Alkalihydroxiden, Ammoniumhydroxid und Aminen.
5. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß als Pyridin-2-ylmethylsulfinyl-1H-benzimidazol Omeprazol, Lansoprazol, Pantoprazol oder Rabeprazol, gewünschtenfalls in Form des Lithium-, Natrium-, Kalium-, Magnesium-, Calcium-, Titan-, Ammonium- oder Guanidiniumsalzes enthalten ist.
6. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß als magensaftresistenter Filmbildner Methacrylsäure/Methacrylsäuremethylester-Copolymerisat verwendet wird.
7. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß die magensaftresistente, dünndarmlösliche Schicht zusätzlich einen Glycerolester enthält.
8. Perorale Arzneimittelzubereitung nach Anspruch 7, dadurch gekennzeichnet, daß als Glycerolester Glycerolmonostearat verwendet wird.

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9. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß auf die magensaftresistente Schicht eine weitere, wasserlösliche Schicht aufgebracht ist.
10. Perorale Arzneimittelzubereitung nach Anspruch 9, dadurch gekennzeichnet, daß die weitere, wasserlösliche Schicht als Filmbildner Hydroxypropylmethylcellulose enthält.
11. Perorale Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß zwischen dem direkt auf den Kern aufgetragenen neutralisierten Filmbildner und dem nicht neutralisierten äußeren Filmbildner bezüglich des Neutralisierungsgrades ein fließender Übergang besteht.
12. Verfahren zur Herstellung einer peroralen Arzneimittelzubereitung in Pellet- oder Tablettenform für säurelabile Pyridin-2-ylmethylsulfinyl-1H-benzimidazole in Form ihrer alkalischen Salze und/oder unter Zusatz von alkalischen Stoffen, dadurch gekennzeichnet, daß direkt auf den Pellet- oder Tablettenkern ein Überzug aus neutralisiertem magensaftresistenten Filmbildner und anschließend darauf ein Überzug aus nicht neutralisiertem magensaftresistenten Filmbildner aufgetragen wird.
13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, daß der Filmbildner aus wäßriger Lösung bzw. Dispersion aufgetragen wird.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07645

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/32 A61K9/36

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 01783 A (ASTRA AB ;BENGTSSON INGA SIV (SE); LOEVGREN KURT INGMAR (SE)) 19 January 1995 see claim 1 see page 7, line 31 - page 8, line 3 see page 9, line 7-12 see page 9, line 16-19 ---	1-8
X	EP 0 244 380 A (HAESSLE AB) 4 November 1987 cited in the application see page 1, line 11 - page 2, line 22 see page 15, line 31 - page 16, line 10 see page 14, line 16 - page 15, line 14 see page 19; example 2 --- -/--	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance  
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Date of the actual completion of the international search

1 March 1999

Date of mailing of the international search report

09/03/1999

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# INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 98/07645

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 232 706 A (PALOMO COLL ALBERTO)  3 August 1993  see claim 1  see column 2, line 13-37  see column 3, line 4-11  see column 3, line 13-21  -----</p>	1-8

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International Application No

PCT/EP 98/07645

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07645

Patent document  
cited in search report

Publication  
date

Patent family  
member(s)

Publication  
date

US 5232706

A

03-08-1993

NONE

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 98/07645

## A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 6 A61K9/32 A61K9/36

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

## B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

## C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	WO 95 01783 A (ASTRA AB ;BENGTSSON INGA SIV (SE); LOEVGREN KURT INGMAR (SE)) 19. Januar 1995 siehe Anspruch 1 siehe Seite 7, Zeile 31 - Seite 8, Zeile 3 siehe Seite 9, Zeile 7-12 siehe Seite 9, Zeile 16-19	1-8
X	EP 0 244 380 A (HAESSLE AB) 4. November 1987 in der Anmeldung erwähnt siehe Seite 1, Zeile 11 - Seite 2, Zeile 22 siehe Seite 15, Zeile 31 - Seite 16, Zeile 10 siehe Seite 14, Zeile 16 - Seite 15, Zeile 14 siehe Seite 19; Beispiel 2	1-8
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☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

\* Besondere Kategorien von angegebenen Veröffentlichungen :

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1. März 1999

Absendedatum des internationalen Recherchenberichts

09/03/1999

Name und Postanschrift der internationalen Recherchenbehörde  
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Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Herrera, S



## C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	US 5 232 706 A (PALOMO COLL ALBERTO) 3. August 1993 siehe Anspruch 1 siehe Spalte 2, Zeile 13-37 siehe Spalte 3, Zeile 4-11 siehe Spalte 3, Zeile 13-21 -----	1-8

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Interne Aktenzeichen

PCT/EP 98/07645

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internes Aktenzeichen

PCT/EP 98/07645

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
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